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A SCIENTIFIC CORNER

WHERE OPTICAL PROBLEMS ARE DISCUSSED AND
THE SOLUTIONS, AS SOLVED BY EXPERIENCE, INDICATED!

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THE INTERMEDIATE ADD

Quite frequently the patient who has been wearing bifocals comfortably for years takes on a new job or acquires a new hobby and finds that the once satisfactory bifocals are not at all successful on the new vocation or avocation.

Concretely, we might cite the case of an office worker whose job was changed to one in which she had to do quite a lot of filing. Her problem, of course, was one of being able to see what she was doing at a comfortable distance. Through the distance portion of her lenses if she could see the filing cabinets she couldn't reach them. Through her reading addition she could see and reach them nicely, but had to hold her head in an unnatural position to do so. Her ophthalmologist suggested a pair of single-vision intermediate glasses to be worn only at this task. In this particular instance, half of the reading addition was added to the distance portion to form the new intermediate pair of glasses. This patient found the intermediate correction not only satisfactory at her work, but it was very useful for doing household tasks such as washing, cooking and ironing.

We sometimes wonder if everyone, whether a business man whose hobby is working around the house—or an office worker—or a housewife—wouldn't be happier optically if, in addition to a well-fitted pair of bifocals, he or she were also fitted with a pair of single vision lenses prescribed at the intermediate range.

"IF IT'S A LENS PROBLEM, LET'S LOOK AT IT TOGETHER"

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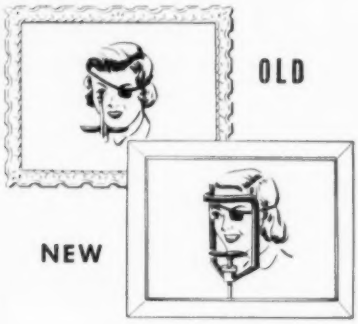

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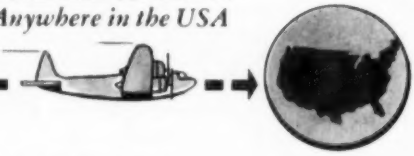

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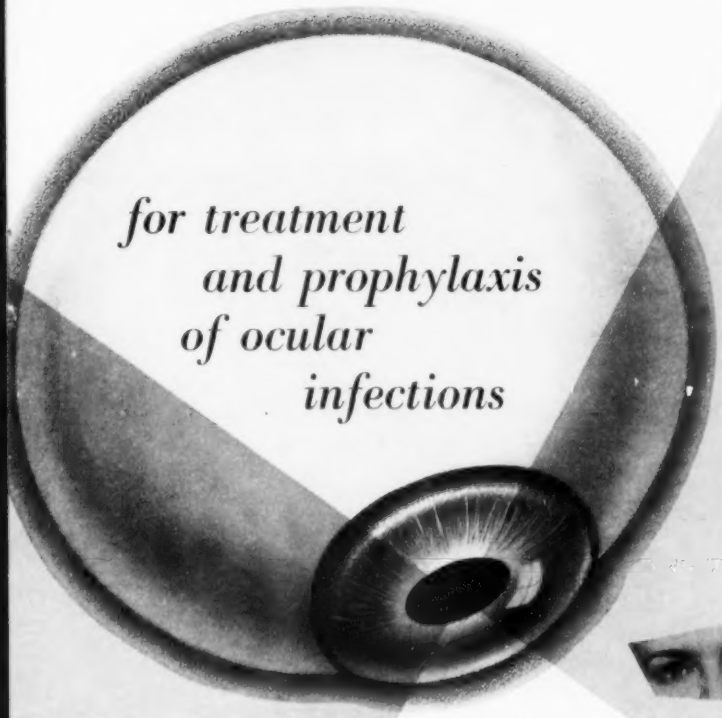

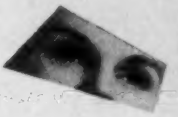

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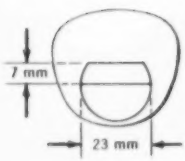

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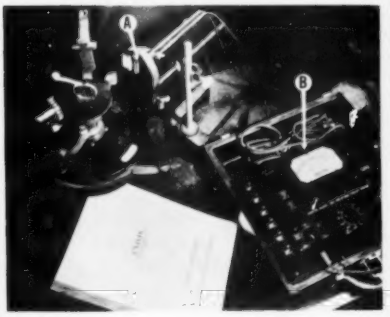


FIG. 1. Showing photo-cell arrangement used to determine amount of light transmission through segment lines. Slotted mask over photo-cell (A) shields cell from all light not coming through untreated 3-foci button. Note relative brightness around edges of slot and reading on meter dial (B)

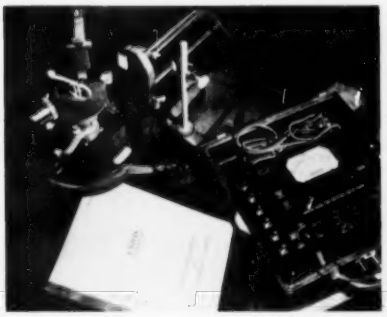
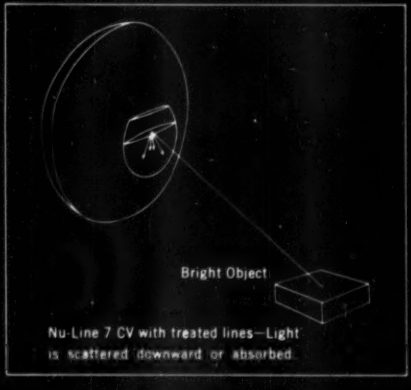
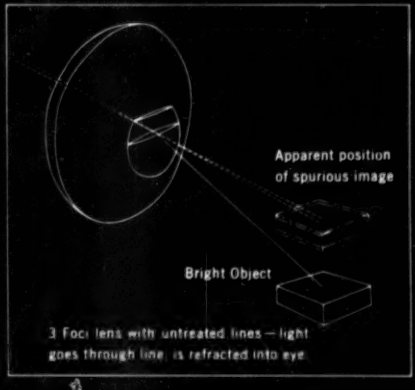


FIG. 2. Arrangement same as Fig. 1, but testing button employed in Nu-Line 7 CV. Note reduction in light around slot and low meter reading.

Here's How



Nu-Line 7 CV with treated lines—Light is scattered downward or absorbed.



3 Foci lens with untreated lines—light goes through line, is refracted into eye.

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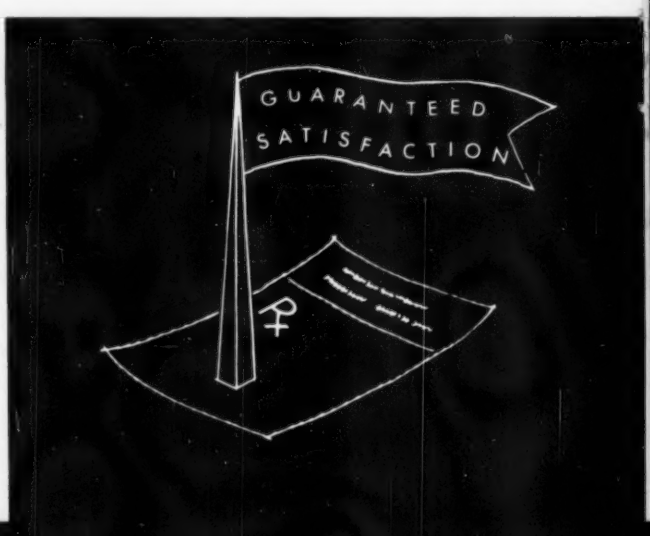

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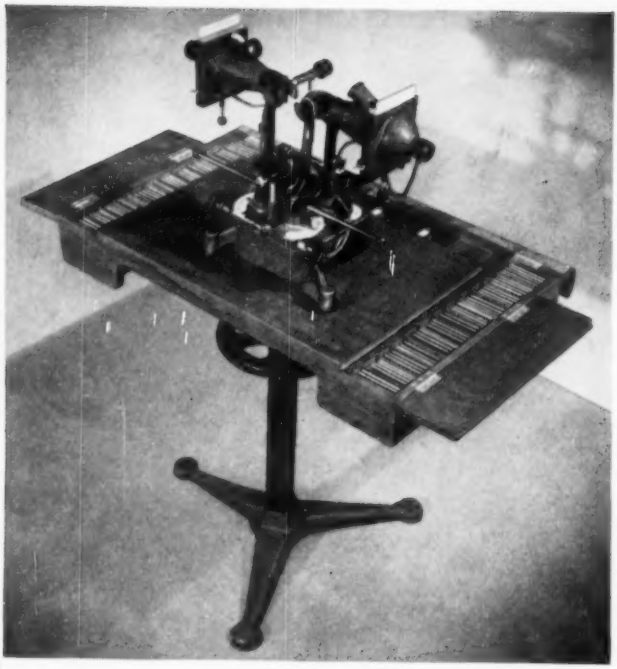

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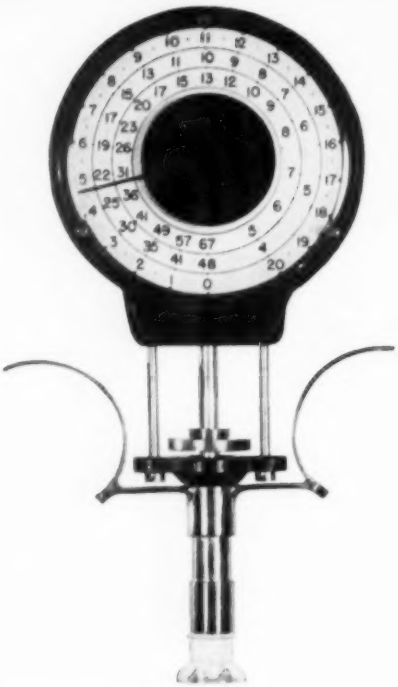

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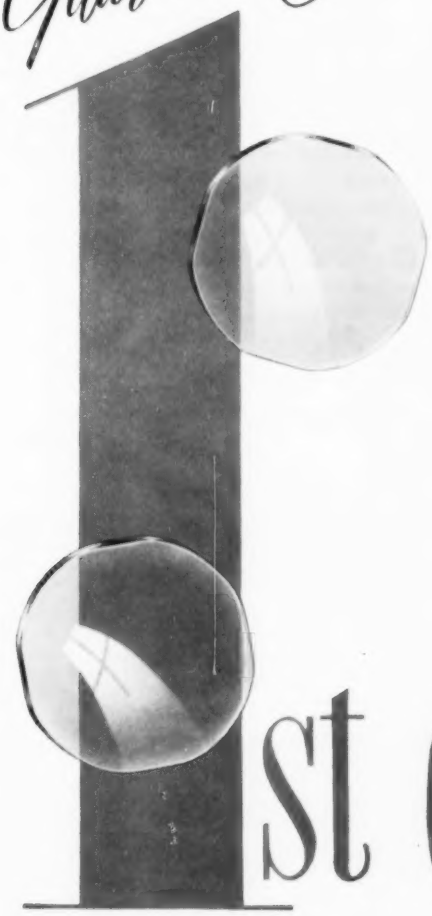

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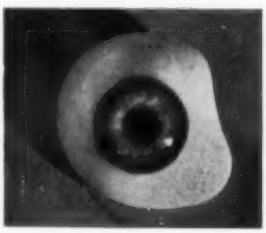

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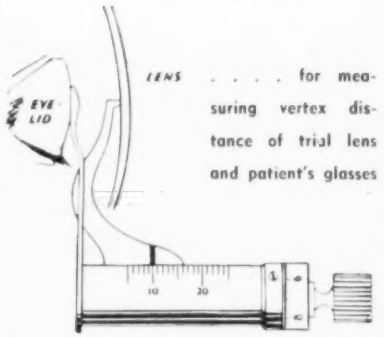

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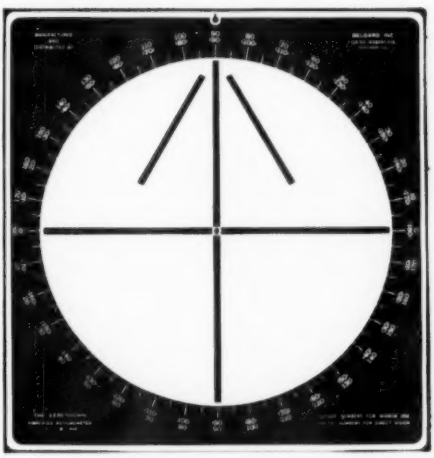

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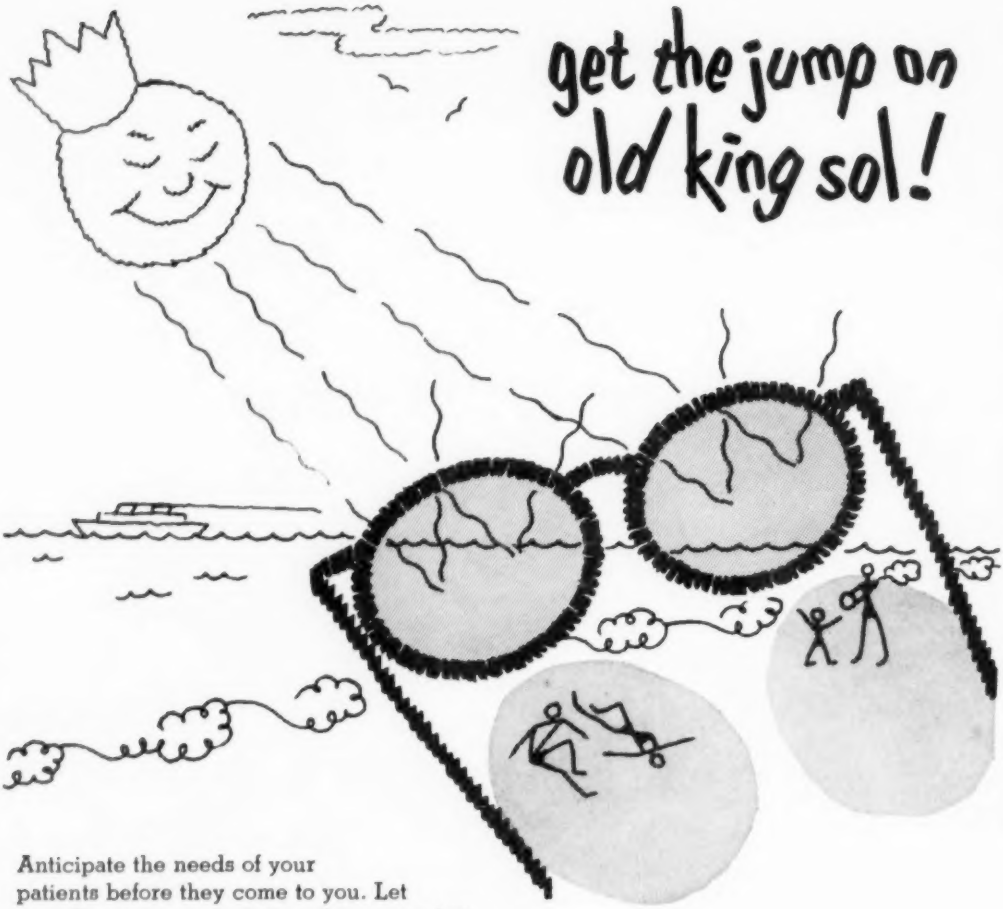

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INFECTIONS OF EYE SOCKET WITH PARTICULAR REFERENCE TO TREATMENT WITH VARIDASE

DAVID W. PARKE, M.D.
AND
JOSEPH M. MILLER, M.D.
FORT HOWARD, MD.

THE LOCAL use of streptokinase-streptodornase (Varidase) offers the surgeon an efficient biologic agent for the treatment of a wide variety of infections. Pus, which contains fibrin and deoxyribonucleoprotein, must be removed to promote healing.

Streptokinase is a catalytic agent which activates plasminogen in the euglobulin fraction of the blood. This causes a liquefaction of fibrin and inhibits the conversion of fibrinogen to fibrin. Streptodornase is a group of enzymes which requires catalytic activation by magnesium or manganese ion and which digests deoxyribonucleoprotein. Sherry, Johnson, and Tillett [5] showed that streptodornase, acting on purified deoxyribonucleic acid and deoxyribonucleic acid in purulent exudates, produced a great fall in viscosity.

Varidase also contains an hyaluronidase,* aproteinase,[1] a ribonuclease,[4] and several nucleotidases and nucleosidases.† The function of these enzymes in the spread of the compounds in the pus and in the digestion of the various substrates is not well known at the present time.

The contents of 1 ampule of Varidase, which contained 107,000 units of streptokinase and 129,000 units of streptodornase, were dissolved in 30 cc. of isotonic solution of sodium chloride. The solution was made fresh every morning. When not in use, the solution was kept in a refrigerator.

Varidase must be placed in direct contact with the area in which its action is desired. When fibrin and deoxyribonucleoprotein are removed from an infected wound, the bacteria in the walls of the site are made more susceptible to the action of the humoral, chemotherapeutic, or antibiotic agents. The phagocytic activity of polymorphonuclear neutrophilic leucocytes in pus has been shown to be considerably enhanced by the depolymerization of deoxyribonucleoprotein, since their clumping is reduced.[3] Effective phagocytosis is dependent upon the presence of living motile polymorphonuclear neutrophilic leucocytes.

Chief, Surgical Service, Veterans Administration (Dr. Miller).

Resident in Ophthalmology, Veterans Administration Hospital (Dr. Parke).

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

* References 5 and 6.

† References 2 and 7.

After digestion of fibrin and deoxyribonucleoprotein has occurred, the products must be removed by washing with an isotonic solution of sodium chloride. The accumulation of these products will delay sterilization and healing of the wound.

Varidase can be used for the treatment of infections in many places. The following reports of two cases show the usefulness of the drug in infections of the orbit.

REPORT OF CASES

CASE I.—A 31-year-old Negro, admitted to the hospital on March 16, 1953, had injuries to the right eye and eyelids, lacerations of the face, multiple fractures of the ribs on the left side, and an injury to the left kidney, with associated shock, sustained about 16 hours previously.

An extensive periorbital ecchymosis and edema of the bulbar and palpebral conjunctivae were present in the right eye. Adequate examination of the globe was impossible because of pain and swelling, although bare light perception was present. The left eye showed a small subconjunctival hematoma nasally and hypertensive retinopathy, Group I. Treatment for shock was started immediately. Penicillin and streptomycin were given systemically, and ophthalmic solution of oxytetracycline (Terramycin) was instilled in the right eye.

The general condition of the patient permitted an exploration and repair of the laceration of the left kidney by suture on March 17. While the patient was anesthetized, the examination of the right eye showed tremendously edematous bulbar and palpebral conjunctivae. Just beneath the insertion of the lateral rectus muscle, there was a linear laceration in the conjunctiva, at the base of which a fibrinous area, 0.3 to 0.4 cm. long, containing black pigment, could be seen. The anterior chamber was filled with blood, which completely obscured the deeper structures.

On March 19, a profuse hemorrhage from the genitourinary tract necessitated a left nephrectomy. A stormy febrile course complicated by a pleural effusion followed. The patient continued to have a mild degree of pain in the eye. The edema of the conjunctivae subsided only moderately. The perception of light continued to be minimal.

On March 27 an enucleation of the right eye was done. A major part of the anterotemporal half of Tenon's capsule and the tendon of the lateral rectus muscle was necrotic. A large organized hematoma lay between Tenon's capsule and the sclera. Evacuation of the hematoma left a soft eye. Although it seemed probable that extrusion would occur later, a 14 mm. plastic ball was inserted, Tenon's capsule being closed with interrupted sutures of 0000 chromic absorbable surgical sutures U. S. P. The rectus muscles were sutured over the capsule, and the friable and edematous conjunctivae were repaired. The eyelids were closed by suture.

Considerable pain and edema were noted during the next three days. On the fourth day a moderate amount of dirty-gray exudate was found. Because of an increased amount of exudate, the sutures in the eyelids were removed on the fifth day. The plastic ball was spontaneously exposed and was removed without difficulty. A culture of the pus was sterile aerobically and anaerobically.

The socket was irrigated with a 1:5,000 aqueous solution of benzalkonuim (Zephiran) hydrochloride three times a day. The instillation of the solutions of oxytetracycline and benzalkonuim was without effect. The systemic administration of oxytetracycline was started. Little change, however, was noted in the degree of edema or the amount of the exudate. The administration of all local medications was stopped. A No. 12 F. rubber catheter was inserted into the socket and taped to the face. The following regimen was carried out every four hours from April 9 through April 15. The socket was irrigated with 5 cc. of isotonic solution of sodium chloride through the catheter. Five cubic centimeters of a solution of Varidase,‡ containing about 17,983 units of streptokinase and about 21,500 units of streptodornase, was injected into the socket through the catheter. The patient remained in the supine position for about one-half hour after each treatment to retain the solution in the socket and to permit digestion of the pus. Because the catheter produced an irritation of the eyelids, it was removed on April 10, when the socket was clean. Thereafter the solutions were put directly into the socket. The edema decreased

‡ The Varidase was supplied by the Lederle Laboratories Division, American Cynamid Company.

partly with progressive cleanliness of the socket. A culture of the exudate on April 14 was sterile aerobically and anaerobically. The patient was discharged from the hospital on April 17, to await the fabrication of a prosthesis.

CASE 2.—A 29-year-old white man, admitted to the hospital on May 4, 1953, had severe pain in the right socket associated with a large amount of mucopurulent pus. Enucleation of a severely injured right eye had been done on June 2, 1948, and a Guyton exoplant was inserted. This gave an excellent cosmetic result, but since implantation of the prosthesis, the patient had had frequent episodes of infection in the socket, associated with a profuse mucopurulent discharge.

The eyelids on the right side were edematous, and a large amount of stringy, purulent pus covered the external surface of the lower lid. The bulbar and palpebral conjunctivae were greatly injected and edematous, so that the Guyton exoplant was completely covered.

A probe was passed around the medial side of the exoplant, and about 2 cc. of pus was released. A culture of the pus was sterile aerobically and anaerobically.

The following regimen was carried out every four hours from May 4 through May 8. The socket was irrigated with 5 cc. of isotonic solution of sodium chloride through the catheter. Five cubic centimeters of a solution of Varidase, containing about 17,983 units of streptokinase and about 21,500 units of streptodornase, was injected into the socket. The patient was kept in the supine position for about one-half hour after each treatment to retain the solution and to permit digestion.

By May 6 the edema had largely subsided, so that the exoplant was well exposed. The pain and the amount of pus decreased. On May 7 the inflammation had resolved to a considerable degree. The exoplant was removed on May 8. After operation, the pain was completely relieved, but a copious discharge of pus recurred. Varidase was instilled into the socket, as before, from May 9 through May 14. A rapid subsidence of edema was observed, and the pus rapidly decreased in amount. The patient was discharged from the hospital on May 14 to await the fabrication of a prosthesis.

SUMMARY

The use of Varidase was associated with an excellent clinical result in two patients with infections of the socket of the eye. Further therapeutic trial of this agent in the treatment of these infections is indicated.

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CORTICOTROPIN, CORTISONE, THYROID, TESTOSTERONE IN SYPHILITIC INTERSTITIAL KERATITIS

JOSEPH V. KLAUDER, M.D.
PHILADELPHIA
AND
GEORGE P. MEYER, M.D.
CAMDEN, N. J.

THIS STUDY reports the results of the treatment of 36 patients (56 affected eyes) with acute syphilitic interstitial keratitis who received one or a combination of the following drugs, corticotropin, cortisone, extract thyroid, and testosterone.

Other treatment, except for the use of mydriatics, was withheld during administration of these agents in order more easily to evaluate their effect; but sooner or later, out of consideration for the welfare of the patient, we resorted to more efficacious therapy, namely, fever and antisyphilitic medicaments. Our previous experience with these older methods served as a control in judging the effectiveness of the newer ones.

Results of treatment were evaluated by the effect on the keratitis: the speed of clearing of the cornea, the time necessary for the eye to become quiet, the rate of improvement in visual acuity, and the best final vision. The real challenge in treatment is the elimination of resultant industrial blindness, which by previous methods of treatment has not been achieved in the severer cases.[10]

The cases were classified as mild, moderate, or severe. This was necessary because evaluation of therapy must be judged mainly by its effectiveness against severe cases. Mild cases often do well with no therapy and rarely result in industrial blindness.

THERAPEUTIC STUDY

Corticotropin (ACTH).—Three patients with severe interstitial keratitis were treated with corticotropin (Cases 2, 3, and 4; Figure). The total doses ranged from 450 to 670 mg., administered in the course of 9 to 15 days. During administration of the drug no other treatment except for a mydriatic was given. There was slight, if any, improvement at the conclusion of treatment. Two of these three patients

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From the Ocular Syphilis Clinic, Wills Eye Hospital, and the Division of Venereal Disease Control, Department of Public Health of Philadelphia.

This investigation was supported by a research grant, B-12 (C5), from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, United States Public Health Service.

(Cases 3 and 4) were then given, as a sole means of treatment, subconjunctival injections of cortisone. There was no striking improvement following these injections.

Cortisone.—Subconjunctival Injections: At the onset of study cortisone was employed by subconjunctival injection, later by local instillation. The injection method comprised administration of 0.05 cc. of an aqueous suspension of cortisone acetate, each cubic centimeter containing 25 mg., daily for three consecutive days. After a rest of several days another course of three injections was given. The total number of injections ranged from three to nine.

In addition to the two patients already discussed, who were treated with corticotropin, four other patients with severe interstitial keratitis received cortisone injections to the exclusion of other treatment except for a mydriatic. In one patient only one of the two affected eyes was injected in treatment. In another patient injection of the second eye was postponed for comparison with the treated eye. In both patients no difference in the course of the disease was apparent in the treated and untreated eyes.

It was concluded that injection of cortisone in the manner employed was of questionable benefit. Cases 3 and 4 are representative of the series. In striking contrast to the high incidence of recurrence of acute interstitial keratitis following cessation of cortisone employed by instillation, only one of the six patients treated by injections had a recurrence. This patient had a recurrence in one of the two affected eyes seven months after injections of cortisone were given in the treatment of both eyes.

Inasmuch as the six patients treated with cortisone by injection were not noticeably helped, fever, thyroid, and antisyphilitic treatment were then given, with resultant acceleration in improvement. The final visual acuity (with correction or with pinhole disk) in the nine affected eyes of these six patients was 6/9, in four eyes; 6/12, in three eyes; 6/15, in one eye, and 6/21, in one eye.

It is doubtful whether corticotropin and cortisone contributed in any way to the favorable outcome in these cases.

Local Instillation: The formula advised by Woods[1] was employed—25 mg. of cortisone acetate per cubic centimeter in a buffered phosphate solution with 1 : 5,000 benzalkonium (Zephiran) chloride as the preservative and spreading agent. One drop was instilled in the conjunctival sac every hour during the day and every two hours throughout the night. This interval was increased as a favorable response was obtained. As a maintenance dose after subsidence of inflammation, one drop was instilled three times daily.

This treatment was first employed early in 1951 and, for reasons to be later discussed, was discontinued in the summer of 1952. In this interval 13 patients, representing 21 affected eyes, were treated. The disease of each affected eye was graded as follows: mild, seven eyes; moderate, six eyes; severe, eight eyes.

Two plans of treatment were employed: 1. Local use of cortisone was discontinued after subsidence of the inflammation, and systemic treatment was continued. 2. Local instillation of cortisone was continued, as well as systemic treatment, after subsidence of the inflammation. Under the latter plan cortisone was given for variable periods; the longest was four months. Under both plans there was a high incidence of recurrence of acute interstitial keratitis after cortisone was discontinued.

Of the 13 patients, 9 had recurrences; of the remaining 4, 1 was lost to observation, and 3 had no recurrence after observation as long as one year.

The severity of recurrence varied, from mild to severe. In some cases the recurrence was more pronounced than the original attack. The interval between cessation of cortisone therapy and recurrence varied; the shortest period was 16 days, the longest was 4 months. Under Plan 1, one patient had four recurrences in a period of five months. Under Plan 2, a patient who had cortisone treatment for four months after subsidence of acute keratitis had a recurrence in one eye 18 days after the medicament was stopped and in the other eye 11 weeks after. The recurrence in each eye of this patient was more pronounced than the initial attack and necessitated additional hospitalization for 51 days.

In the treatment of the first attack of this patient, penicillin was given, in addition to cortisone. Cortisone was purposely not used in the treatment of the recurrences, but fever and thyroid were administered, and subsequently testosterone. Final visual acuity was 6/12 in the right eye and 6/9 in the left eye.

Similar recurrences after discontinuance of the topical use of cortisone were reported by Woods,[2] Crane and McPherson,[3] and Oksala.[4] The patient reported by Oksala had four recurrences in nine months, and one recurrence was severer than the original attack. Oksala noted absence of deep blood vessels during the use of cortisone.

Drews, Barton, and Mikkelsen [5] reported on 17 patients treated topically with cortisone. Since relapse occurred after the medicament was discontinued in the first three patients, these authors employed a daily maintenance dose (cortisone in ointment). They wrote:

> No patient who has adhered to this program has yet developed a recurrence, although one discontinued topical cortisone against advice after eight months of therapy, and relapsed 10 days later. Since maintenance therapy has not been deliberately discontinued in these cases, there is as yet no indication of what the final recurrence rate may be.

(Apparently the patients were still on the maintenance dose when the paper was published.)

Results of Topical Cortisone Treatment: In mild and moderate cases there was a dramatic clearing of the cornea and subsidence of inflammation, in as brief a period as 7 to 12 days, without formation of the salmon patch. With no other treatment have we observed such a rapid effect on acute interstitial keratitis. Because of recurrences this dramatic effect, however, was not maintained. We are in accord with Woods's [2] observation that such a striking effect does not occur in severe cases of the disease. Drews, Barton, and Mikkelsen [5] wrote: "An occasional severe case may still require artificial fever therapy."

Slit-lamp examination of patients treated topically with cortisone showed the absence of superficial blood vessels that constitute the so-called salmon patch.* Vascularization has long been stressed as a propitious process, and the appearance of the salmon patch heralds beginning retrogression of the disease. Spicer [7] appropriately wrote:

> When the whole cornea has become vescular and the vessels have met at its center, a rapid change, a crisis, occurs; in a very short time the vessels begin to shrink, the signs of irritation

* There is general agreement that corneal vascularization can be inhibited and wound healing retarded by topical application of cortisone, as observed by Irvine and Irvine [6] in experimental studies.

come to end, the cornea begins to clear—the attack is over. The rapidity of this change is often very remarkable, an interval in one case of seven days ensued between the height of the attack with all blood vessels engorged to their fullest extent and the almost complete shrinkage of the vessels and the reappearance of something resembling a cornea.

In our cortisone-treated patients recurrences were not prevented by systemic treatment, regardless of whether the systemic treatment was given at the beginning of therapy or only after cortisone was stopped. This suggests that the mechanism that brings interstitial keratitis to an end is consummated in the cornea—in all probability an immunologic process in which vascularization is concerned. Cortisone, obviously, does not assist this mechanism, but retards it. In this sense cortisone is not curative, and this idea is consistent with the results of its use, as well as that of corticotropin, in treatment of other diseases.

The failure of systemic treatment in preventing relapse of interstitial keratitis after cessation of cortisone therapy emphasizes the role of local processes in the modus operandi of curing the disease. This finding supports the opinion of many ophthalmologists who have long maintained that interstitial keratitis is a self-limited disease and is but little, or not at all, influenced by antisyphilitic treatment. There is additional evidence of the truth of such a view—the failure of any treatment in preventing involvement of the second eye, recurrences in the same eye, and, for that matter, the initial attack of the disease. Moreover, during systemic therapy this paradox may occur: retrogression of the disease in the first eye, while the second eye becomes progressively worse.

Objections to the Use of Cortisone: We regard cortisone as of doubtful value in relieving the severer grades of interstitial keratitis. The percentage of recurrences with noncortisone therapy varied from 10 to 20%.† With cortisone it is much higher, hence entailing longer hospitalization and greater expense and incapacitation.

Nor is it known how long cortisone must be used to prevent relapse, or even whether it could prevent recurrence at all. We feel that the use of cortisone prevents the development of local immunity and cure. For these several reasons we have discontinued its use.

Thyroid Therapy.—Earlier investigators, notably Cedercreutz,[12] Enroth,[13] and Fuchs,[14] employed extract of thyroid in the treatment of interstitial keratitis. The results of our endocrine studies[15] of patients with interstitial keratitis rationalize the use of thyroid gland. Although there was no clinical evidence of hypothyroidism or myxedema in our patients, laboratory studies indicated thyroid deficiency. In our study, the trend of the basal metabolic rate was low (—15% and below in 41 of the previously reported 88 patients, and again illustrated in Cases 1, 3, and 4), and there was, in a certain percentage of patients, correlation of these low values with other tests of deficient thyroid function: low protein-bound iodine in serum (Cases 1, 2, and 3) and low and low-normal radioactive iodine uptake of the thyroid gland. There was, however, no correlation of low metabolic rates with high values for serum cholesterol.

In the treatment of the acute phase of the disease, we gave orally 2 to 3 grains (0.12 to 0.2 gm.) daily of desiccated thyroid, together with fever therapy (Cases 1, 2, 3, and 4). This dosage was continued until there was improvement, as evi-

† References 7 through 11.

denced by clearing of the cornea, lessening of the opacities, and recession of superficial blood vessels. We have administered this dose for a few weeks to two months. In slowly progressive cases (in the postcrisis stage, as later discussed) we have administered a second course of thyroid extract for about one month. We never saw toxic reactions from this dosage. Since we observed a uniform low basal metabolic rate in the patients studied, we now dispense with determination of the rate before administration of thyroid. Thyroid is likewise given in recurrences and with involvement of the second eye.

The following is a schematic case record of a patient with severe interstitial keratitis who received fever, thyroid, and metal chemotherapy. The effect was the most rapid we observed with this method of treatment, although the final favorable visual results were achieved in other patients similarly treated.

Fever Therapy.—As employed in the present study, this therapy embraced 4 to 6 fever treatments for the mild grade of interstitial keratitis, about 8 for the moderate grade (Case 5), and 12 to 14 for the severe grade (temperature rises to

CASE 1.—*Eleanor Y.; age 17*

		Vision
Hospital admission	O.D. : 2 mo.	O.U. : H.M.
10/31/49 to	O.S. : 1 wk.	
11/23/49	11 fever rises, 101-104 F.; 7 soluble bismuth injections; 4 arsphenamine injections; thyroid, grains 2 to 3	O.D. : 3/60 O.S. : C.F.
Discharge from hospital		
12/7/49	Thyroid stopped; O.U. almost quiet	O.D. : 6/21 O.S. : 6/30
1/16/50	Corneas much clearer	O.D. : 6/9; pinhole 6/9 + 3 O.S. : 6/30; pinhole 6/15
Before thyroid	Basal metabolic rate	— 12%
	Protein-bound iodine of serum	3.6 γ per 100 cc. (4 to 8 γ normal)
After thyroid	Protein-bound iodine of serum	10.9 γ per 100 cc.
9/19/52	No recurrence	O.D. : 6/9, cc 6/6 O.S. : 6/12, cc 6/12 + 2

less than 100 F. were not considered; Cases 1, 2, 3, and 4). In cases of slowly progressive severe interstitial keratitis, after the patient's discharge from the hospital we have given a second course of four to six fever treatments. Such patients were usually ambulatory.

We have found Pyrifer the most satisfactory fever-producing agent. This is a Bacillus coli vaccine, made in Switzerland. It comes as a series of ampules numbered 1 to 7. It is given intravenously every other day in ascending strengths. After the injection of No. 1 ampule, the next higher serial number is administered at each injection. In order to administer more than seven fever treatments, the dose in ampule No. 7 is repeated. Calculation of dosage is, therefore, unnecessary; temperature rises are uniformly produced with a minimum of other systemic symptoms (headache, chill, malaise). We have employed fever therapy in ambulatory patients provided they could get home in about one hour and remain in bed until their temperature became normal.

Fever therapy is resumed in the treatment of recurrences and in involvement of the second eye.

Metal Chemotherapy.—As aforementioned, we regard antisyphilitic treatment of acute interstitial keratitis as of little benefit to the cornea and advise against its employment as a sole means of treatment.

In a previous communication,[16] we reviewed evidence suggesting that interstitial keratitis is not solely a syphilitic process and discussed the shortcomings of antisyphilitic treatment. The opinion was expressed that better medicaments in treatment would not be treponemicidal.‡ We also reported on the deliberate withholding of all treatment (except a mydriatic) in mild cases of interstitial keratitis, and good final results ensued.

Since the underlying syphilitic infection requires antisyphilitic therapy (with improvement of the general state of health), we routinely employ it in cases of acute interstitial keratitis. Penicillin combined with fever therapy has not given results superior to those achieved with metal chemotherapy and fever.[16] We prefer metal chemotherapy in the acute stage, since there is evidence that arsenicals, bismuth, and mercury in treatment of inflammatory processes of the anterior uveal tract have a nonspecific beneficial effect.§

On the other hand, there is no evidence of any beneficial nonspecific effect with penicillin. We therefore administer alternating courses of oxophenarsine (Mapharsen) and a bismuth compound during the acute phase of the disease. The first course is a weekly injection of oxophenarsine for eight consecutive weeks. Conjointly for the first two to three weeks a biweekly injection of a soluble bismuth compound (bismuth sodium tartrate) is administered (Cases 1, 2, 3, 4, and 5). After the course of oxophenarsine, a course of an oil suspension of bismuth (bismuth subsalicylate) is employed. After the keratitis becomes quiescent, penicillin is then employed, as it shortens the period of antisyphilitic treatment. We give 6,000,000 units of procaine penicillin G in oil with *2%* aluminum monostearate in the course of 14 days.

Testosterone.—This substance was employed in the treatment of interstitial keratitis, as there is evidence of endocrinologic imbalance in this disease. We have observed less acne in cases of interstitial keratitis than in controls.[15] The hormonal mechanism that favors acne apparently is inimical to the development of interstitial keratitis. Acne is related to excess of androgen or a disturbance of androgen-estrogen balance, and in acne there is a trend toward a low urinary output of 17-ketosteroids.‖ Males exhibit both a greater severity of acne and higher levels of urinary androgens than do females—hence the lessened relative incidence of interstitial keratitis in males (1:3). The estrogenic overactivity of girls from 8 to 15 years of age or the underactivity of androgenic (adrenocortical and/or gonadal) function makes the peak of incidence of onset of this disease fall typically in the prepubertal years and affects the female more than the male.

‡ Interestingly, Cangé and Antoine[17] prophesied that future studies would more firmly establish an endocrinologic basis of interstitial keratitis and that organotherapy would become a rational method of treatment.

§ This reason is comparable to the rationalization of older ophthalmologists in the use of mercury for various ocular inflammatory processes. For example, Chance[18] wrote: "Our knowledge of the value of the mercurials in inflammation is clinical rather than experimental, empirical rather than scientific, yet it is based upon the general judgment of the profession after countless daily observed facts, and it seems scarcely possible that it is not correct." Lucic[19] may also be cited in this connection.

‖ References 20 and 21.

Before terminating this study, we could treat but three patients, all females, with testosterone.¶ The first, aged 14, received 25 mg. of testosterone cyclopentylpropionate, given intramuscularly at weekly intervals for six injections; the second, aged 16, received two courses of four injections, with a rest period of one month between each course. These two were receiving antisyphilitic treatment and had completed treatment with fever and thyroid. Their interstitial keratitis had improved; further progress was slow, and inflammatory symptoms were still present at the time of testosterone treatment. The testosterone did not appear to affect the keratitis; the quiescent stage eventually ensued. Final visual acuity for the four affected eyes of these two patients ranged from 6/15 to 6/9.

The third patient, aged 17, had severe untreated bilateral keratitis. Visual acuity was reduced to perception of hand movements in each eye. On admission, treatment with testosterone was initiated, to the exclusion of other systemic treatment. Three injections of 25 mg. each were administered in the ensuing 10 days. Then, fever and thyroid treatment and metal chemotherapy were instituted. During

Corrected Final Visual Acuity in Each of Fifty-Six Affected Eyes of Thirty-Six Patients Classified According to Degree of Involvement and Treatment Received*

Treatment †	No. of Patients	Degree of Involvement	No. of Eyes	Visual Acuity				
				6/6	6/9	6/12	6/15	6/21
Thyroid; fever	17	Severe	10	2	1	4	3	..
		Moderate	11	3	4	3	1	..
		Mild	4	4	..	..	..	..
Cortisone; fever	7	Severe	2	..	..	2	..	..
		Moderate	4	2	2	..	..	..
		Mild	5	..	4	1	..	..
Cortisone; thyroid	12	Severe	16	..	6	5	4	1
		Moderate	2	1	..	1	..	..
		Mild	2	..	1	1	..	..

* The figures below visual acuity represent the number of eyes with that visual acuity.
† The specified treatment is detailed in the text. In addition to that specified, all patients received antisyphilitic therapy, either penicillin, or, more usually, metal chemotherapy.

the latter part of this treatment, methyl testosterone (Oreton-M) was given orally, 50 to 75 mg. three times a week for one month. Urinary excretion of 17-ketosteroids increased from 8.3 to 15.4 mg. per 24 hours (normal, 5 to 15 mg.). There was no apparent effect on the keratitis. (This patient is not included in the accompanying Table, since keratitis is still active and final visual acuity has not yet been evaluated.)# The only untoward effect of testosterone therapy of the three patients was disturbance of the menstrual cycle during testosterone administration, and the appearance of a sparing number of acne lesions in the third patient treated. The appearance of the latter was doubtless consistent with the increase of urinary excretion of 17-ketosteroids.

Practical Consideration in Treatment and Prognosis.—It is of the utmost importance to initiate treatment in the inflammatory stage. Systemic therapy in

¶ Since the incidence of interstitial keratitis in our clinic is decreasing, it will be difficult in the near future properly to evaluate testosterone therapy and to study further androgen-estrogen relations in interstitial keratitis.

As this article goes to press, corrected visual acuity of this patient (now 12 months from onset of the keratitis) is 6/15 in both eyes.

the quiescent stage of the disease directed toward clearing residual corneal opacities is of doubtful value.

As aforementioned, we believe the appearance of superficial blood vessels comprising the salmon patch heralds the beginning retrogression of the disease. Sometimes thereafter (two to five weeks), inflammatory symptoms begin to subside, and there is evidence of clearing of the cornea and diminution of opacities. This is well described by Spicer under the term of "crisis." This stage of beginning retrogression cannot always be determined at a single inspection. It requires repeated observations for one week or longer for one to be certain of the diminution of the inflammatory process.

Beyond this stage of beginning retrogression, further progress is very variable; it may be rapid, as stated by Spicer, or it may be weeks or months before quiescence ensues. Treatment administered beyond the stage of the "crisis" is, in our experience, of questionable value. Although we continued metal chemotherapy and have given additional fever and thyroid therapy in the postcrisis stage, as aforementioned, we are not convinced that such treatment hastens the stage of quiescence. The greatest benefit of systemic treatment is achieved in the precrisis stage. We regard as unnecessary attempts to hasten the stage of quiescence if absorption of opacities and clearing of the cornea keep pace with subsidence of ciliary injection. In this event we regard the prognosis as good. On the other hand, if clearing of the cornea does not keep pace with subsidence of ciliary injection, the end-result is quiescence with a variable degree of opacification of the cornea, ranging up to leucoma. Apparently, after the stage of quiescence, absorption of corneal opacities is not initiated. The latter apparently occurs in the precrisis stage and continues to a variable degree after quiescence. If inflammation is regressing, the quiescent stage is approaching. We believe, for the aforementioned reasons, that it is justifiable to try to delay quiescence of the disease in an attempt to augment regression of corneal opacities. This is a new approach in the treatment of interstitial keratitis. Such delaying procedures could include, among others, the local use of ethylmorphine hydrochloride (Dionin), treatment with the thermophore, subconjunctival injections of hypertonic saline solution, Pregl's solution * and, possibly, sterile milk.

We have had as yet no opportunity to try out these therapeutic ideas.

Results of Treatment.—The Table shows results in terms of corrected final visual acuity (determined at least one year after quiescence) in each of the 56 affected eyes of the 36 patients classified according to the severity of the disease and the treatment received. If the mild and moderate cases of interstitial keratitis are disregarded in the analysis of results and only the severe cases are considered, the Table shows that of 28 eyes with severe interstitial keratitis the poorest final visual acuity was 6/21. Although this number is relatively small, the result we regard as commendable, since none had industrial blindness. As aforementioned, in no other report embracing a large number of cases unclassified as to severity of involvement has industrial blindness been eliminated as an end-result following treatment.

In a previous communication,[16] a report was made of final visual acuity, with correction, of 97 affected eyes of 59 patients with acute interstitial keratitis treated

* An antiseptic solution of the sodium salt of hydriotic acid and iodic acid with iodine (0.04%).

with penicillin alone or with penicillin plus artificial fever. Over 10% in each group became industrially blind.

The common denominator in treatment employed in this study was fever and antisyphilitic medication, given to all patients, and then thyroid, given to 29 of the 36 patients. Of the seven patients who did not receive thyroid (Case 5 is one of the seven), the disease was mild or moderate (as shown in the Table) in all but one. The final visual acuity of this one patient, who had severe bilateral keratitis, was 6/12 in each eye.

Apparently, fever and antisyphilitic therapy does not account for the favorable results achieved in this study, as shown in the Table. The supplemental treatment with thyroid is suggested as the explanation. In support of this view is the result shown in Case 1 and the apparent effect of the thyroid in Cases 2, 3, and 4, and in still other cases the records of which are not detailed in this report.

We know of no report of treatment of a series of cases of acute interstitial keratitis in which thyroid was employed, or, as aforementioned, in which the severity of the disease was considered and classified in the analysis of final results.

We are compelled, for the reasons presented, to leave undecided the value of testosterone as a supplement to fever and thyroid therapy. The benefit of its use in our three patients is difficult to evaluate in the absence of any striking result.

Pending further study of testosterone, our future treatment will comprise fever, thyroid, and antisyphilitic treatment. A large number of severe cases of interstitial keratitis than are here reported must be studied to make more valid the opinion that supplemental treatment with thyroid eliminates industrial blindness as the end-result of the disease.

REPORT OF CASES

CASE 2.—*Severe interstitial keratitis treated with corticotropin and subsequently with fever and thyroid.*

A. G. (L4478), a white youth aged 14, was admitted May 11, 1950. He had severe bilateral interstitial keratitis of five weeks' duration in the left eye and of two weeks' duration in the right eye.

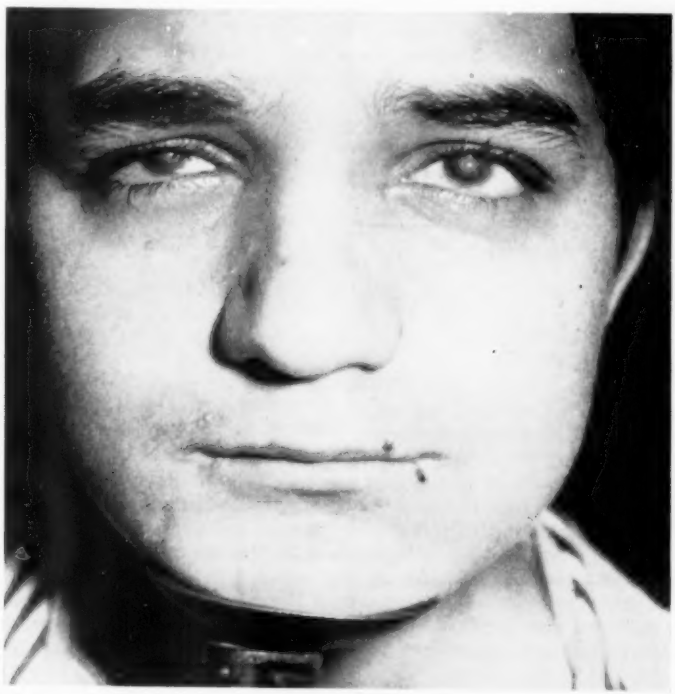
He had stigmas of congenital syphilis and serous synovitis (Clutton's joint) of the right knee. The S. T. S. was strongly positive. The basal metabolic rate was —3%; protein-bound iodine of the serum was 3.6 γ per 100 cc. (normal 4 to 8 γ); the urinary excretion of 17-ketosteroids in 24 hours was 10.7 mg.* The absolute count of eosinophiles before injection of 20 mg. of corticotropin was 300 per cubic millimeter, and four hours after the injection it was 135.

Both corneas were diffusely involved with active infiltration, which coalesced into a solid plaque in the pupillary area. This central plaque was more pronounced in the left eye. Neither iris could be seen; ciliary injection and subjective symptoms were pronounced. Slit-lamp microscopy confirmed the diagnosis of syphilitic interstitial keratitis. Visual acuity was reduced to perception of hand movements in the right eye and to counting fingers in the left eye.

Except for a mydriatic, treatment consisted solely of corticotropin, first given on May 13 and last on May 28. At the onset 20 mg. three times daily was administered; later this dose was given daily, and on May 27 and 28 a 10 mg. dose was given daily. The total dose was 670 mg. On May 25 it was questionable whether there was any improvement of the right eye; visual acuity was reduced to perception of hand movements. The left eye, however, showed some lessening of the plaque in the center of the cornea; the periphery was appreciably clearer; the iris was dimly visible; subjective symptoms and ciliary injection was appreciably improved;

* The method of Holtorff and Koch[22] was employed. Normal values were regarded as 8 to 20 mg. per 24 hours for men and 5 to 15 for women.

visual acuity was ½/60. There was no change in the swelling of the right knee. His appetite improved considerably; he gained 6 lb. (2.7 kg.) in weight, and he had a rounded, so-called "moon face" and presented a few acne lesions. In the absence of striking improvement, it was felt that, on ethical grounds, more reliable treatment should be started. On May 25 the following treatment was instituted: fever produced by Pyrifer given intravenously every other day; thyroid, 2 grains (0.13 gm.) daily; oxophenarsine weekly, and soluble bismuth compound twice weekly. After one week of this treatment improvement was obvious; visual acuity in the right eye remained limited to hand movements; vision in the left eye was 6/60, and with the pinhole 6/30. On June 18 (date of discharge) the patient had had 12 fever sessions; thyroid therapy had been continued. The periphery of both corneas was considerably clearer; the irises were visible,



Photograph (Case 2), showing "moon face," a few acne lesions on the lip and chin, and leucomatous infiltration of the corneas, after administration of 670 mg. of corticotropin. Subsequently, fever, thyroid, and metal chemotherapy were administered. Final corrected visual acuity (three years after onset of keratitis) was 6/12 in the right eye and 6/12 +3 in the left eye.

the central opacities were regressing; inflammatory symptoms had disappeared. This improvement is apparent in the Figure, taken on June 12. Visual acuity was 6/60 in the right eye (with pinhole 6/30) and 6/21 in the left eye (with pinhole 6/15). Swelling of the right knee was unchanged; the left knee became swollen about June 1. Acne lesions were still present.

The patient was discharged to the care of an ophthalmologist in another city, with the suggestion that metal chemotherapy be discontinued after two months. On Feb. 15, 1951, the physician reported that both corneas showed extensive nebulae with deep vascularization. The eyes were quiet. Visual acuity in the right eye was 6/30, with pinhole 6/15; in the left eye 6/45, with pinhole 6/21. In July, 1953, corrected visual acuity was 6/12 in the right eye and 6/12 + 3 in the left eye.

CASE 3.—*Severe interstitial keratitis treated with corticotropin and subsequently with fever, thyroid, and cortisone.*

R. H. (L4491), a Negro girl aged 12, was admitted June 1, 1950, with severe bilateral interstitial keratitis of about one month's duration. The attack was the initial one and had been untreated.

She had stigmas of congenital syphilis and unilateral serous synovitis (Clutton's joint). The S.T.S. was strongly positive. The basal metabolic rate was —30%; protein-bound iodine of serum was 5.0 γ per 100 cc.; urinary excretion of 17-ketosteroids in 24 hours was 3.2 mg. The absolute eosinophile count before injection of epinephrine was 81 per cubic millimeter, and four hours after injection it was 38.

Both corneas were diffusely infiltrated, with thick plaques in the central two-thirds. The irises could not be seen. Lacrimation, photophobia, and ciliary injection were severe. Visual acuity in each eye was reduced to counting fingers at 2 ft. (60 cm.).

From June 3 to June 10 corticotropin was used, to the exclusion (except for a mydriatic) of other treatment. Twenty milligrams was given three times daily except on June 10, when 10 mg. was given three times a day. The total dose was 450 mg.

On June 10, the keratitis of the right eye was slightly improved, and the infiltration was appreciably less, especially in the periphery. An indistinct view of the iris was then possible. There was no change in the left eye or in the swelling of the right knee. Visual acuity in each eye was equal to counting fingers at 2 ft.

Fever therapy (Pyrifer) was started on June 11 and ended on July 10. The total number of fever sessions was 14. Thyroid was given from June 8 to July 24. At the onset, 2 grains was given daily; later, 3 grains (0.195 gm.). Weekly injections of oxophenarsine and biweekly injections of a soluble bismuth compound were started on June 12. As of July 12 there was definite, but not striking, improvement of the corneas. Visual acuity in the right eye was 1/60; in the left eye 1½/60. There was no change in the swelling of the right knee, and the left knee was not affected.

Subconjunctival daily injections of cortisone (as discussed in the text) was initiated on July 10, in the left eye only, for a total of three injections. No benefit from such injection was apparent on comparison with the untreated eye. Cortisone injection in the right eye was then initiated, for a total of three injections. There was likewise no striking benefit from such injection. Then both eyes were treated daily for three consecutive injections (last one, July 23). As of Aug. 7, improvement had slowly continued, corneal opacities were less and no longer confluent, the irises were then visible, and ciliary injection and subjective symptoms were less. Visual acuity in both eyes was 6/60, with pinhole 6/30. The patient was discharged from the hospital on July 26.

Both eyes became quiescent in the latter part of November. Visual acuity on Nov. 20 was 6/21 in the right eye, with pinhole 6/15 — 1, and 6/21 — 1 in the left eye, with pinhole 6/12. Only metal chemotherapy was continued. In June, 1952, corrected visual acuity was 6/12 in each eye.

CASE 4.—*Severe interstitial keratitis treated with corticotropin and subsequently with cortisone with fever and thyroid.*

B. R. (L4505), a Negro woman aged 18, was admitted on June 29, 1950, with severe unilateral interstitial keratitis of the right eye of one month's duration. The disease had been untreated, and the attack was the initial one.

The S.T.S. was strongly positive. The basal metabolic rate was —16%. Urinary excretion of 17-ketosteroids was 11.7 mg. in 24 hours. The face was devoid of comedones and of acne vulgaris. All but the periphery of the cornea was heavily infiltrated; photophobia, lacrimation, and ciliary injection were pronounced. Slit-lamp microscopy confirmed the diagnosis of interstitial keratitis of the syphilitic type. Visual acuity of the right eye was limited to hand movements. The left eye was uninvolved; visual acuity was 6/9.

Corticotropin was given from July 3 to July 12, for a total of 660 mg. At the onset 20 mg. was administered every six hours; on July 10 and July 11, every eight hours, and on July 12 one injection was given. On July 12 improvement of the keratitis was questionable; however, visual acuity was 1/60. During corticotropin therapy the eosinophile count ranged from 0 to 19 per cubic millimeter.

Subconjunctival injections of cortisone (as discussed in the text) were instituted on July 10, for three consecutive daily injections.

Another course of consecutive daily injections was given on July 16, July 17, and July 18, and a third course on July 22, July 23, and July 24. On July 24 there was slight improvement of the inflammatory process. Visual acuity varied from 1/60 to 3/60.

Fever therapy was started on July 25, and thyroid was given—at first, 2 grains daily, and later, 3 grains; injections of oxophenarsine were given weekly and of a soluble bismuth compound twice a week. On Aug. 18 fever therapy was discontinued; the patient had had 13 fever treatments. Thyroid therapy was discontinued on Aug. 28. At termination of fever therapy, subjective symptoms, ciliary injection, and corneal opacities were less pronounced. Visual acuity was 6/15, with pinhole 6/21. Retrogression of the keratitis continued, until the eye became quiescent about the middle of October. Visual acuity at that time was 6/21, with pinhole 6/9; and in January, 1951, it was 6/12, with pinhole 6/9 + 2.

CASE 5.—*Bilateral keratitis; recurrence in eye in which topical cortisone was not continued.*

M. W. (I.4671), a white girl aged 11 years, three weeks prior to admission, on Aug. 2, 1951, had been hit in the left eye with a towel. From this time inflammation persisted, until a diagnosis of interstitial keratitis was made three weeks later.†

She had stigmas of congenital syphilis and unilateral serous synovitis (Clutton's joint). The S.T.S. was strongly positive.

The patient had bilateral interstitial keratitis. She was unaware of the mild involvement of the right eye. Visual acuity was 6/9. Involvement of the left eye was graded as moderate; there was a circinate opacity in the center of the cornea with moderate surrounding haziness; ciliary injection, photophobia, and lacrimation were moderate. Visual acuity was 6/30. Slit-lamp microscopy showed absence of deep blood vessels.

Cortisone was employed locally (as discussed in the text); at the onset one drop was instilled in the conjunctival sac of each eye every hour during the day and every two hours during the night; later the interval was increased. It was employed in both eyes from Aug. 2 to her discharge from the hospital, on Aug. 18. In addition, fever therapy (Pyrifer) was administered for a total of nine fever inductions, with temperatures ranging from 101 to 106 F. A soluble bismuth compound was injected twice weekly and oxophenarsine once weekly.

Visual acuity was 6/6 in the right eye and 6/15 in the left eye. Her mother was advised to instill cortisone in each eye three times daily.

The patient was again admitted to the hospital on Oct. 22, 1953, for recurrence of active interstitial keratitis of the right eye only. Through a misunderstanding, cortisone had been instilled only in the left eye. Involvement of the right eye was now graded as moderate, though initially it was mild. Visual acuity in this eye was 6/21; in the left eye, 6/6. Slit-lamp microscopy showed absence of deep blood vessels.

During hospitalization, of 14 days, cortisone instillation was resumed in the right eye and continued in the left eye. Fever therapy, comprising five fever sessions, was administered, and also 2,400,000 units of penicillin. Cortisone was discontinued Dec. 10, 1952. Slit-lamp microscopy in January, 1952, still showed absence of deep blood vessels. In October, 1952, there had been no recurrence. Corrected visual acuity in the right eye was 6/9 — 1; in the left eye, 6/6. In April, 1953, there had been no recurrence; deep blood vessels were still absent, and visual acuity was 6/6 — 4 in the right eye and 6/6 in the left eye.

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† Discussion of the role of trauma in precipitating interstitial keratitis is afforded in a previous paper.[23]

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METASTATIC CARCINOMA OF THE CHOROID (BRONCHOGENIC) SIMULATING PRIMARY TUMOR OF THE EYE

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AND
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A CASE of primary bronchogenic epidermoid carcinoma with metastasis to the choroid is reported because of unusual clinical and pathologic aspects. The patient, admitted primarily because of hemoptysis and the roentgenographic finding of a shadow in the right lung, was found to have an intraocular mass which had the appearance of a primary tumor of the choroid. The choroidal tumor increased rapidly in size and produced uncontrollable pain, necessitating enucleation. The histologic appearance of the choroidal tumor gave rise to a diversity of diagnoses. Only at necropsy were the primary site and histologic nature of the tumor established.

This case is of interest because of the rarity of metastatic carcinoma of the eye, its simulation of a primary tumor of the choroid, and the unusual histologic structure of the tumor in the choroid.

REPORT OF A CASE

F. A. R. (R 139889), a 53-year-old white man, was admitted on July 31, 1951. His presenting complaints were hemoptysis and abdominal pain. He was a heavy smoker (40 cigarettes a day). He had had a cigarette cough for 20 years. In 1947 he was told that a "spot on his lung" was apparent on roentgenographic examination, but he refused further study. One month prior to admission he noted flecks of bright-red blood in his sputum. In the course of the month before admission he lost 20 lb. (9 kg.) in weight and noted exertional dyspnea.

On physical examination the liver was found to be enlarged, irregular, firm, and tender. Roentgenographic examination revealed a mass in the upper lobe of the right lung and a radiolucent defect in the left frontal bone.

On Aug. 8, 1951, the patient was referred to the eye clinic because he complained of pain in the right eye. Visual acuity was 6/5 in each eye. A large retinal detachment, with steep margins, with no hole, and dark on transillumination, was found in the lower half of the right eye. A corresponding field defect was demonstrated.

The ophthalmologists were of the opinion that the patient had a primary melanoma of the choroid. The question then arose whether the pulmonary and hepatic lesions were metastases from the eye.

Bronchoscopic examination on Aug. 9 was negative. A liver biopsy on Aug. 27 was reported as showing a highly anaplastic metastatic carcinoma. The primary site could not be determined from the histologic structure of the tumor. It was, however, not suggestive of a melanoma.

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The retinal detachment increased rapidly in size. By Sept. 10 visual acuity in the right eye was reduced to perception of hand movements temporally. The patient began to experience severe and intractable pain in the right eye. By Sept. 16 he required 100 mg. of meperidine hydrochloride every three hours, without obtaining complete relief of pain. Accordingly, an enucleation was performed on Sept. 18. The specimen showed a large mass in the choroid inferiorly, extending from the optic nerve to the pars plana of the ciliary body (Fig. 1). There was a small amount of serous fluid between the tumor and the detached retina and ciliary body. Microscopically, the neoplasm in the choroid consisted of small islands of closely packed tumor cells separated by large areas of hemorrhage. The tumor was highly anaplastic and was composed

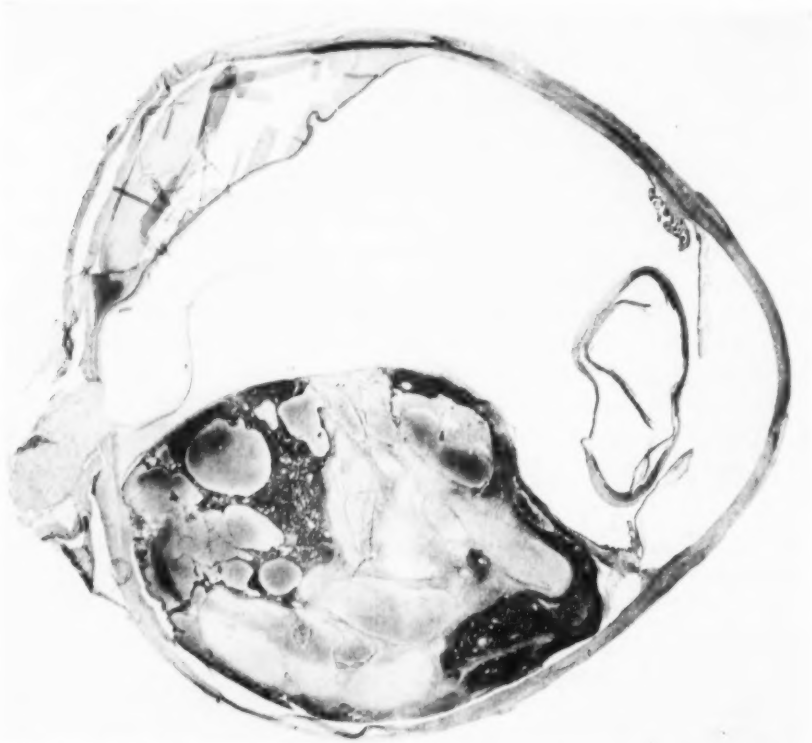

Fig. 1.—Metastatic tumors in choroid, right eye. Hematoxylin and eosin stain; × 5.

of round or oval-shaped cells with large vesicular nuclei and indistinct cytoplasm. Mitotic figures were numerous, and enlarged bizarre hyperchromatic nuclei were fairly common. Multinucleated giant tumor cells were frequently encountered. The tumor cells were supported by a scant, delicate fibrillar connective tissue stroma. An outstanding feature in all parts of the neoplasm was the presence of pseudorosettes, which were produced by a circular grouping of tumor cells (Fig. 2). Scattered through the tumor were a moderate number of hemosiderin-laden macrophages and a few lymphocytes.

The eye sections were reviewed by a number of general and ophthalmic pathologists, who suggested a variety of opinions, among which were malignant melanoma, neuroblastoma, and retinoblastoma.

The patient became progressively worse, developed generalized metastases, and died on Jan. 27, 1952.

Postmortem Examination (four hours after death).—The midportion of the bronchus to the right upper lobe was markedly narrowed by a primary tumor, which invaded the bronchial wall and extended to the lung parenchyma. The right upper lobe was almost entirely replaced by a dense tumor mass. Small discrete tumor nodules were seen in the right lower lobe and in both lobes of the left lung.

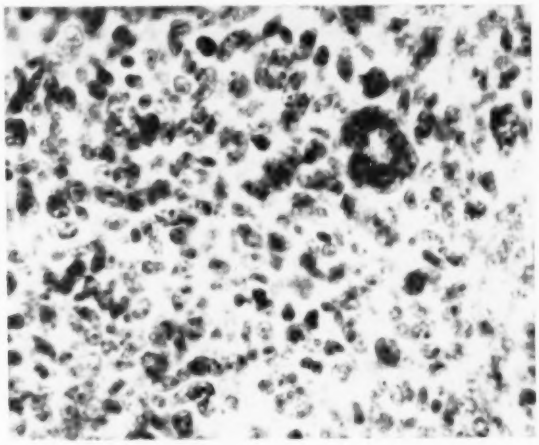

Fig. 2.—Detail of tumor in choroid, right eye, showing pseudorosette. Hematoxylin and eosin stain; × 760.

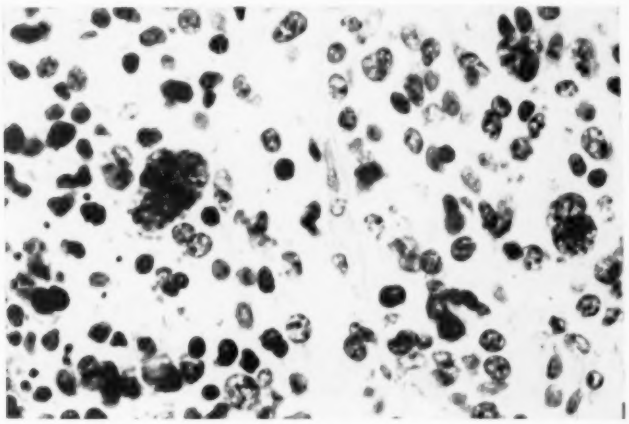

Fig. 3.—Photomicrograph of primary tumor in bronchus of right upper lobe, showing anaplasia of the tumor, and multinucleated giant tumor cells. Hematoxylin and eosin stain; × 760.

The liver was greatly enlarged (weight, 6,300 gm.) and contained innumerable small and large metastatic tumor nodules. In aggregate the tumor replaced about four-fifths of the liver parenchyma. Metastatic tumor was also found in the wall of the right atrium of the heart, both kidneys, both adrenals, the pituitary gland, the dura mater, and the skull. The hilar and peribronchial lymph nodes, and the abdominal, mesenteric, and retroaortic nodes were partly or wholly replaced by tumor.

Microscopic Observations.—The tumor in the right upper lobe bronchus was highly anaplastic and consisted of large round cells with vesicular nuclei and scant, ill-defined cytoplasm. Mitotic figures and multinucleated tumor giant cells were numerous (Fig. 3). There was a striking lymphatic spread of tumor throughout both lungs. Many of the perivascular and peribronchial lymphatics were distended and filled with tumor cells. Some of the metastatic tumor

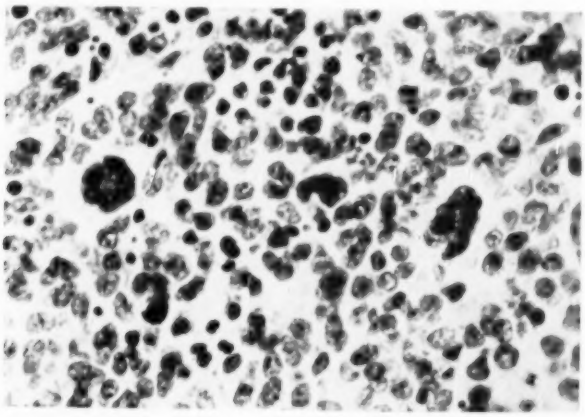

Fig. 4.—Metastatic tumor in left lung with pseudorosettes. Hematoxylin and eosin stain; × 510.

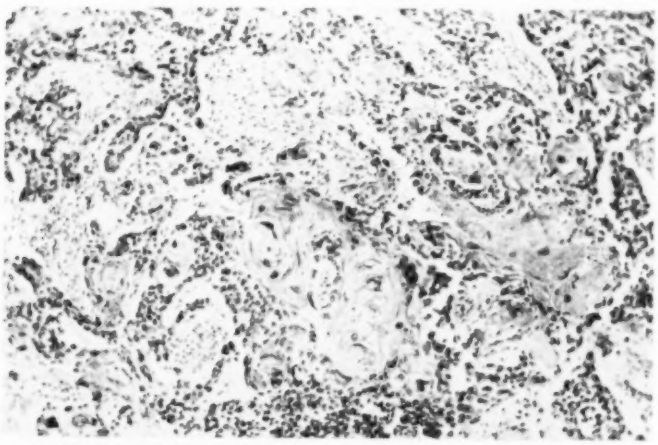

Fig. 5.—Metastatic tumor in adrenal gland, showing many epithelial and keratin pearls. Hematoxylin and eosin stain; × 96.

nodules in the right lower lobe and the left lung showed extreme vascularity, containing many large and small thin-walled spaces filled with blood. Several of these nodules also contained pseudorosettes, closely resembling those seen in the choroidal tumor (Fig. 4).

Pseudorosettes were found in the liver metastases. Here, also, the vascularity of the tumor nodules and the lymphatic spread throughout the liver were conspicuous.

In contrast to the bronchial tumor and the metastases elsewhere, the tumor nodules in the adrenals, the kidneys, and the mesenteric lymph nodes showed collections of epithelial pearls

and keratin pearls (Fig. 5). This finding, together with the gross observation of tumor in the right upper lobe bronchus, clearly established the basic structure of the neoplasm as a bronchogenic epidermoid carcinoma with widespread metastases.

COMMENT

Metastatic carcinoma of the eye is infrequent.* Stallard,[4] from the records of the Royal London Ophthalmic Hospital Clinic, estimates the incidence at 1 : 140,000. Duke-Elder [5] suggests that metastases to the eye may be more frequent than would appear from the literature. He points out that routine fundus examination in patients with carcinomatosis is usually omitted because of the grave general condition. He also cites the frequent omission of pathological examination of the eyes when these patients come to necropsy. Godtfredtsen,[7] however, in a large series of cases of cancer in which routine fundus examination was performed still finds metastases to the choroid to be rare.

Metastases to the choroid are hematogenous, and in 25% of the cases bilateral.[1] Metastasis to the choroid is a late event. The posterior short ciliary arteries are the usual path of entry into the eye. This accounts for the predilection of intraocular metastases of carcinomata for the posterior pole of the eye. The secondary deposit is usually flat and saucer-shaped, and thins out toward the equator. Elevation exceeding 2 mm. is rare. Metastatic carcinoma of the choroid causes pain without glaucoma,[6] probably as a result of pressure by the tumor tissue on the ciliary nerves.

In the later stages, the tumor may simulate a primary tumor of the choroid, producing retinal detachment, glaucoma, inflammation of the optic nerve and sclera, and perforation of the globe.

The metastasis usually reproduces the structure of the primary growth. Hemorrhage is common.

The site of the primary growth is most frequently the breast; next in order of frequency are the lungs, alimentary tract, thyroid, prostate, and adrenal.

The present case is of interest both from its clinical and from its pathologic aspects. Although primary and secondary tumors of the choroid differ in their ophthalmoscopic appearance, confusion may occur, as in the present case.

The formation of pseudorosettes in bronchogenic epidermoid carcinoma definitely occurs, but is not common. Their presence in this case resulted in the erroneous diagnosis of primary tumor of the choroid. The finding of epithelial and keratin pearls in other metastatic deposits confirmed the bronchial origin of the tumor. There was no evidence of keratinization in the metastases with rosettes.

SUMMARY

A case of bronchogenic epidermoid carcinoma with metastasis to the choroid is presented. The choroidal metastasis simulated a primary tumor on ophthalmoscopic examination. Histologically the choroidal tumor was highly anaplastic and gave no clue as to the primary site. The presence of pseudorosettes led to an erroneous diagnosis of primary tumor of the eye. On necropsy the finding of epithelial and keratin pearls in metastatic lesions elsewhere, as well as a primary bronchogenic epidermoid carcinoma, established the lungs as the source of the choroidal tumor.

1100 Grand Concourse (56).

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AN IMPROVED GONIOSCOPIC CONTACT PRISM

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THE GONIOSCOPIC contact prism shown in Figure 1 incorporates four internal reflecting surfaces to facilitate examination of the angle of the anterior chamber of the eye. Such an improvement over the original prism, described in 1945,[1] had been attempted before the first publication, but the speculum could not retain the heavy prism against the cornea. A subsequent change in the design of the speculum would have overcome this difficulty, but advantage was not taken of this opportunity until 1951, when a second mirror [2] was added in a successful modification of the original design. Thorpe's instrument required fewer manipulations and thus shortened and simplified the examination. The instrument described here is a further step in the same direction, made possible by redesigning several of the mechanical features of the device.

The new instrument consists of the prism (*A*, Fig. 1); a speculum (*B*), with a spherical flange (*a*) to fit under the lids against the globe, a shelf (*b*) to keep the upper lid and brow tissues away from the prism, and a handle (*c*) which keeps the lower lid away from the prism and serves for manipulation, and two springs (*C*) which support the prism properly relative to the speculum.

As in both preceding models, the prism itself is made of acrylic resin because of its weight advantage over glass.* It is in the form of a four-sided pyramid, truncated by a concave, spherical surface near its peak. The truncating surface contacts the cornea of the eye; the four sides act as internal reflecting surfaces, beyond which quadrants of the chamber angle are imaged, and the base forms the surface, through which the images pass at near-right angles to reach the observer.

Figure 2 represents a schematic cross section of the prism in place against the eye. Concave surface (*a*), with a radius of curvature of 8.2 mm., contacts the cornea only. An interposed capillary film of suitable fluid creates optical continuity between the plastic and the transparent tissue of the eye. Flat surfaces *b* and *c* are two of the four internally reflecting surfaces, set at an angle of 60 degrees to each other and each at an angle of 60 degrees from the front plano surface (*d*). A ray of light from object O_1 in the upper chamber angle passes with little refraction to point r_1, from which it is reflected out through the front surface of the prism to the observer at I_1. The same principle applies to a ray of light from O_2 in the lower chamber angle,

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* Bausch & Lomb Optical Co., Rochester 2, N. Y.

being reflected from r_2 on the opposite reflecting surface and reaching the observer at a new vantage point (I_2), about 14 mm. above the first vantage point. The other two reflecting surfaces of the prism are related in this same manner to each other.

This arrangement of surfaces makes it unnecessary to rotate the prism except for a few degrees, and this only in rare instances. When the prism is centered on the cornea, the entire circumference of the chamber angle will reveal itself without

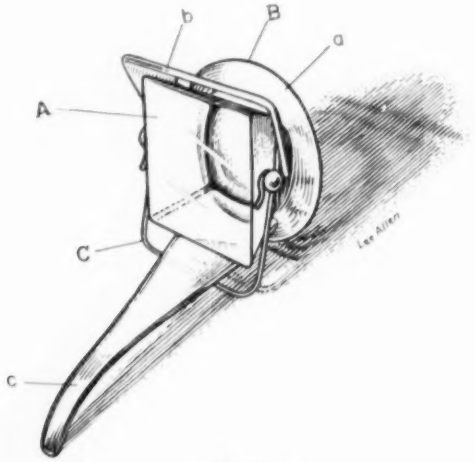

Figure 1.

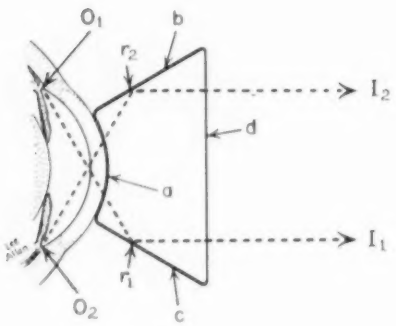

Figure 2.

magnification to an observer's eye located ahead of and approximately in the axis of the observed eye. Figure 3 is a photograph demonstrating this gross appearance. Each mirror surface reveals a portion of the angle on the opposite side of the cornea. Thus the superior quadrant of the chamber angle is seen in the lower mirror (*a*), the inferior quadrant in the upper mirror (*b*), the temporal quadrant in the mirror on the nasal side (*c*), and the nasal quadrant in the temporal mirror (*d*). The direct frontal view of the iris and pupil (*e*) is a separate image and is of value only for orientation of the gonioscopic images.

If it is desirable to examine carefully an area which lies to one end of the mirror image, the prism, speculum and all, may be rotated a few degrees by gently swinging the handle pendulum-fashion to one side to bring the area into full view. After each such manipulation the handle must be returned to its normal position directly below the pupil.

The most complete and accurate visualization of the chamber angle is obtained with the slit-lamp biomicroscope, furnishing magnification and controlled illumination through the gonioscopic prism. For this examination 1 drop of 0.5% tetracaine is instilled twice, with a one-minute interval, into the eye to be examined. The patient is comfortably situated at the slit lamp, and the biomicroscope and slit beam

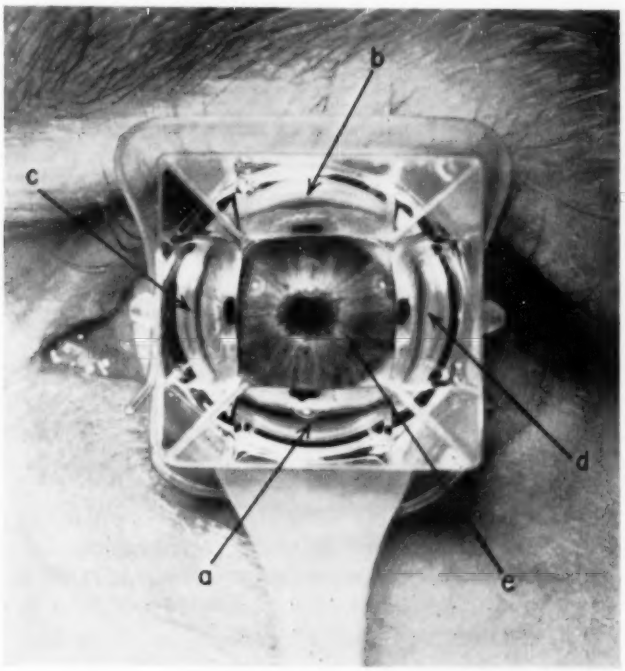

Figure 3.

are focused upon the eye before the gonioscopic prism is introduced. The slit-lamp beam is made as nearly coaxial with the biomicroscope as possible. The patient is asked to remove his head from the head rest. One-half drop of 0.5% or 1% methylcellulose in isotonic saline solution is placed upon the concave surface of the prism. The patient is asked to look downward, and while the upper lid is held up with one hand, the spherical flange of the speculum is introduced under the lid. (If the patient tries to squeeze the eye shut at this point, the shelf [*b*, Fig. 1] may be firmly gripped from above between the thumb and the middle finger, while the index finger extends downward against the handle and the instrument is held slightly up and away from the globe until the orbicularis muscle is felt to relax.) The patient is then asked to look straight ahead, while the lower lid is brought out in

front of the spherical flange. It is advisable to pull the lower lid tissues well forward and manipulate them to be certain a roll of conjunctiva is not pinched between the speculum and the globe, because such pinching can result in discomfort to the patient both during and following the examination.

If there is any question that the lids will retain the prism, it is best to support the device with the hand during the rest of the procedure. However, in most young and many older persons the speculum may be released, at least for moderate lengths of time.

The patient's head is guided into the head rest to avoid bumping against the forehead rest or side-supports, and the observer takes his normal position for the slit-lamp examination. While looking over or around the biomicroscope, the examiner places one of his elbows on the slit-lamp base and, resting the little finger and back of the hand against the patient's cheek, gently grasps the very tip of the speculum handle between the index and the middle finger. Slight but constant pressure is exerted upward and back against the eye. This guarantees contact of the prism against the cornea. Manipulation of the handle changes the angle of view into the chamber angle. While first locating the proper image, the large anterior surface of the prism should be aligned at right angles to the axis of the subject's eye and to the midline of the biomicroscope.

If the direct view of the pupil and iris is the first brought to focus, the biomicroscope should be lowered 6 or 7 mm. to the region of the lower mirror in order to find the image of the superior quadrant of the chamber angle. By raising the biomicroscope from this point about 14 mm., the image of the inferior quadrant will be located in the upper mirror. From this point the biomicroscope may be brought back to the central reference image and shifted 6 or 7 mm. to either side for viewing a lateral quadrant. (A broad beam should be used in this last instance as it simplifies the location of the area; and if a Goldmann or a Koeppe mirror is available, it should be used. Otherwise sclerotic scatter is recommended as the easiest type of illumination in the lateral angles.)

The broader expanse of anterior surface in the new prism has made both binocular viewing and illumination of the lateral angles much easier than before, but some experience must be gained before these are mastered. It will be found that directing the biomicroscope into the prism at a slight angle to one side or the other from normal may often improve the binocular view.

When the speculum is being removed from the eye, it should be done in such a way that the patient cannot squeeze suddenly and scrape the edge of the spherical flange across the cornea.

The instrument may be sterilized by submersion in 1:1,000 benzalkonium (Zephiran) chloride aqueous solution. Common germicidal solutions for sterilizing metal instruments must never be used. Alcohol is a slow solvent, and must not be used. Concentrations of fumes from ether, chloroform, etc., will permanently damage the optical surfaces of the prism.

Soap and water applied by a long-bristled camel hair brush is recommended for washing the inaccessible parts of the instrument, while only the soapy finger tips should be used to wash the two exposed optical surfaces. All soap must be rinsed off with water, never more than lukewarm. Never dry the optical surfaces with cloth or other harsh, fibrous material. Use soft, clean chamois skin for this purpose and replace with new when it begins to harden from use.

ADDENDUM

Harvey E. Thorpe, M.D.

EXAMINATION OF THE CENTRAL RETINA AND DEEP VITREOUS WITH THE GONIOPRISM

The central part of the new four-sided gonioprism has proved useful for slit-lamp microscopic examination of the macular and perimacular area of the retina. The field of view encompasses an area approximately 3-4 disc diameters across. By rocking the gonioprism either vertically or laterally, additional areas are brought into view. The narrow beam (sharply focused) is employed for producing an optical section of the retina. A clear view is readily obtained. This helps to outline macular cysts, early macular degeneration and holes, microaneurysms, waxy exudates, colloid excrescences, circumscribed retinal edema, small hemorrhages within, beneath, or in front of the retina, etc. Both direct focal and proximal (indirect) illumination are employed. Moderate dilatation of the pupil (5-6 mm.) suffices for central retinal examination by this technique. The illumination beam is set at a very acute angle to the microscope axis (10-12 degrees). The rhomboidal reduction prism of the Goldmann Haag-Streit Slit Lamp can be employed to accomplish such narrowing between the axes of illumination and observation. Similar narrow angulation is readily accomplished by the illuminating system of the new Zeiss Opton Slit Lamp and the English Allied Instrument Makers Slit Lamp.

The deep vitreous can also be studied by this technique. Vitreous shrinkage, detachment, and collapse can readily be recognized with the aid of the central portion of the four-mirror gonioprism. Direct focal illumination, the oscillating or scanning beam, and retroillumination are employed.

In the above technique the gonioprism serves the purpose of a flat-surfaced contact lens. But it has some advantages in that the speculum mount prevents the eyelids from smearing the front surface of the gonioprism. Such smearing occurs as a rule with the usual flat-surface corneal lenses contact employed for deep vitreous study. The gonioprism can readily be kept in alignment with the cornea, whereas the flat corneal contact lens often sags.

EXAMINATION OF THE EXTREME RETINAL PERIPHERY, CILIARY BODY, AND LENS EQUATOR WITH THE FOUR-SIDED GONIOPRISM

The mirror surfaces of the gonioprism can be employed for viewing the extreme retinal periphery and the equatorial region of the crystalline lens. The pupil should be dilated maximally for this technique. The light beam is reflected into the desired segment of the retinal periphery by choosing the mirror surface opposite the area to be examined. The microscope view is directed into the same mirror surface used for illumination. "Cycloscopy" of the ciliary body can thus be accomplished, viewing the pars plana and the ora serrata. After iridectomy, especially in aphakics, a beautiful view with optical section is obtained of the innermost layers of the corona ciliaris and adjoining vitreous. Hans Goldmann, of Berne, designed a large three-mirror contact lens for peripheral ophthalmoscopy. It is considerably more difficult to keep in place than the gonioprism.

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NUTRITIONAL DYSTROPHY OF THE CORNEAL EPITHELIUM

Report of Additional Cases with Biochemical Examinations

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SUBSEQUENT to a preliminary report made on nutritional dystrophy of the corneal epithelium,[1] facilities for examination of the blood and urine for various vitamins, viz., vitamin A and carotene in the blood and thiamine and riboflavin in the urine, were made available through the courtesy of the Institute of Nutrition, Department of Health, Republic of the Philippines.

While at the time of the preliminary report the impression was entertained that such a type of corneal dystrophy was of nutritional origin, and while therapeutic tests seem to bear out the assumption that it was due to hypovitaminosis in the B complex group, nevertheless, the absence of supportive biochemical examinations precluded definite conclusions as to the etiology.

The cases covered by this report were seen in Lucena, Philippines, within the period from September, 1950, to August, 1952, inclusive, and in a number of them examinations have been made for blood level and urinary excretion of some vitamins. It is intended in this report to establish a relationship between corneal dystrophy of this type and the vitamin state of the patient.

STATISTICS OF CASES

A total of 24 cases of epithelial dystrophy of the cornea were observed within the 24-month period covered by this report. Of these patients, 19, or 79%, were females (in the preliminary report 73.8% were females).

Ages ranged from 18 to 45 years, with the average age 30.6 years (30.2 years in the preliminary report).

Thirteen of the patients were breast feeding, or the equivalent of 54.1% of the women in the group (62.9% in the preliminary report).

Of the 24 patients seen, however, only 14 were able to report to the Institute of Nutrition for the necessary biochemical examinations. This small number was not through choice of cases, but was influenced solely by the ability of the patients to make the trip to Manila, where the institute was situated—a distance of 140 km. (approximately 87 miles). Of these 14 patients, 1 failed to return for follow-up study after treatment was started, leaving 13 as the total number of cases upon which we could report in further detail.

REPORT OF CASES

CASE 1.—L. P. (Sept. 18, 1950), a 40-year-old married woman, had had foggy vision and numbness of the extremities for one year, or since the time that she had to be confined to bed with advanced pulmonary tuberculosis. Both eyes showed corneal epithelial dystrophy, with this distribution:

Right Left

V.O.D. was 10/200 and V.O.S. was 10/200.

Biochemical Examinations

Vitamin A blood level	24 γ/100 ml.
Carotene blood level	68 γ/100 ml.
Urinary excretion of thiamine	12 γ/gm. creatinine
Urinary excretion of riboflavin	26 γ/gm. creatinine

Intramuscular injections of B complex vitamins (thiamine 30 mg.; riboflavin 10 mg.; nicotinamide 100 mg.; calcium pantothenate 5 mg., and pyridoxine 5 mg.) were given daily. By Oct. 3 (after two weeks) V.O.D. was 20/60 and V.O.S. was 20/120, and the corneal lesions were reduced to half their previous number. By Oct. 18, V.O.D. was 20/30 and V.O.S. was 20/50; by Oct. 30, vision in both eyes were 20/20, and both corneas were clear.

CASE 2.—G. N. (Sept. 18, 1950), a 45-year-old man, had had foggy vision for one month. No subjective or objective signs of polyneuropathy were observed. Both eyes showed characteristic dystrophic lesions of the corneal epithelium distributed in this manner:

Right Left

V.O.D. was 20/260, corrected with + 1.50 D. sph. to 20/60; V.O.S. was 20/60—, corrected with + 1.00 D. sph. to 20/50 —.

Biochemical Examinations

Vitamin A blood level	25 γ/100 ml.
Carotene blood level	61 γ/100 ml.
Urinary excretion of thiamine	9 γ/gm. creatinine
Urinary excretion of riboflavin	106 γ/gm. creatinine

Intramuscular injections of the vitamin B complex were given daily. By Oct. 9, V.O.D. was 20/30, corrected with + 0.50 D. sph. to 20/20. With a similar correction, vision in the left eye was also 20/20. Both corneas at this time were clear.

CASE 3.—N. M. (Nov. 6, 1950), a 32-year-old married woman, had had foggy vision for six months and was breast feeding an 8-month-old child. There were paraesthesias of sock-and-

glove distribution and circumoral numbness. She had had similar complaints on Dec. 1, 1947, after childbirth, for which a diagnosis of nutritional corneal epithelial dystrophy was made in this clinic. The condition was rapidly improved to normal with vitamin B complex. The eyes at the present examination showed the characteristic corneal dystrophy with this distribution:

Right Left

V.O.D. was 20/60 and V.O.S. was 20/60 —.

Biochemical Examinations

Vitamin A blood level	28 γ/100 ml.
Carotene blood level	68 γ/100 ml.
Urinary excretion of thiamine	34 γ/gm. creatinine
Urinary excretion of riboflavin	49 γ/gm. creatinine

With parenteral vitamin B complex therapy, by Dec. 11, 1950, vision in both eyes was 20/20, with no more signs of dystrophy.

Case 4.—R. R. (Feb. 7, 1951), a 35-year-old married woman, had had foggy vision, numbness of the extremities, and angular stomatitis for five months. She was breast feeding a 10-month-old child. The right and left eyes showed corneal stipplings, distributed thus:

Right Left

Vision was 20/200 — in each eye. She had a centrocecal scotoma for 2/1000 white; hence a diagnosis of nutritional dystrophy of the corneal epithelium and nutritional retrobulbar neuropathy was made.

Biochemical Examinations

Vitamin A blood level	27 γ/100 ml.
Carotene blood level	26 γ/100 ml.
Urinary excretion of thiamine	24 γ/gm. creatinine
Urinary excretion of riboflavin	74 γ/gm. creatinine

Serum riboflavin was also determined, giving a level of 2.4 γ per 100 ml. She was given B complex vitamins parenterally up to April, 1951, when vision in each eye was 20/60, with no more corneal stippling and with the centrocecal scotoma reduced to a central scotoma for 1/1000 white. She has since failed to report for follow-up observation of the scotoma.

CASE 5.—G. R. (Feb. 6, 1951), a 25-year-old married woman, had had foggy vision for five months and was breast feeding a 6-month-old child. She had numbness of the extremities and angular stomatitis. Both eyes had the characteristic corneal stipplings, but with a peculiar distribution, thus:

Right Left

Vision was 20/50 on the right and 20/50 — on the left. There was no sign of increased limbal vascularization.

Biochemical Examinations

Vitamin A blood level	38 γ/100 ml.
Carotene blood level	45 γ/100 ml.
Urinary excretion of thiamine	19 γ/gm. creatinine
Urinary excretion of riboflavin	44 γ/gm. creatinine

Serum riboflavin was also determined at 2.1 γ per 100 ml. B complex vitamin therapy was given parenterally, with improvement, so that by March 5, 1951, vision was restored to a normal 20/20 in both eyes and the dystrophic changes had disappeared.

CASE 6.—C. O. (Feb. 20, 1951), a 26-year-old married woman, had had foggy vision since the beginning of the last trimester of pregnancy and was breast feeding a 2-month-old child. She complained further of glare, had maceration of the external canthus of both eyes, and angular stomatitis. Both eyes showed corneal stipplings, with this distribution:

Right Left

V.O.D. was 20/30 and V.O.S. 20/30 —.

Biochemical Examinations

Vitamin A blood level	23 γ/100 ml.
Carotene blood level	23 γ/100 ml.
Urinary excretion of thiamine	20 γ/gm. creatinine
Urinary excretion of riboflavin	36 γ/gm. creatinine

The serum riboflavin was 2.9 γ per 100 ml. Vitamin B complex therapy was instituted, and by March 17, 1951, vision was 20/20 in both eyes. Both corneas had become clear by that time.

CASE 7.—C. C. (Feb. 19, 1951), a 27-year-old married woman, had had foggy vision for one month and was breast feeding a 9-month-old child. Both eyes showed corneal epithelial dystrophy, with the following distribution:

Right Left

Vision in both eyes was 20/120, corrected with + 1.00 sph. ⊂ + 0.50 cyl. axis 180 to 20/20 —.

Biochemical Examinations

Vitamin A blood level	31 γ/100 ml.
Carotene blood level	30 γ/100 ml.
Urinary excretion of thiamine	24 γ/gm. creatinine
Urinary excretion of riboflavin	62 γ/gm. creatinine

With administration of B complex vitamins parenterally, the dystrophy had disappeared by March 17, 1951, and vision for both eyes was 20/40, corrected with + 1.00 sph. ⊂ + 0.50. cyl. axis 180 to 20/20.

CASE 8.—M. L. (May 16, 1951), a 40-year-old married woman, had had foggy vision for six months. She was breast feeding a 1-year-old child. She had had angular stomatitis and maceration of the external canthi of both eyes since delivery. Numbness of the extremities was complained of. Both eyes showed corneal epithelial stipplings, with the following distribution:

Right Left

There was increased vascularization of the limbus of both eyes. V.O.D. was 20/60 — and V. O. S. 20/60.

Biochemical Examinations

Vitamin A blood level	5 γ/100 ml.
Carotene blood level	30 γ/100 ml.
Urinary excretion of thiamine	125 γ/gm. creatinine
Urinary excretion of riboflavin	121 γ/gm. creatinine

The blood level of riboflavin was only 1.9 γ per 100 ml.

With parenteral administration of vitamin B complex, by May 29, 1951, vision in both eyes was 20/20, and the maceration of the external canthi, dystrophic changes in the cornea, and the angular stomatitis, together with the numbness of the extremities, had all disappeared.

CASE 9.—U. R. (June 20, 1951), a 23-year-old married woman, had had foggy vision for nine months and was breast feeding a 10-month-old child. Both eyes showed corneal epithelial changes, with this distribution:

Right Left

V.O.D. was 20/60, and V.O.S. was 20/40 —.

Biochemical Examinations

Vitamin A blood level	11 γ/100 ml.
Carotene blood level	70 γ/100 ml.
Urinary excretion of thiamine	10 γ/gm. creatinine
Urinary excretion of riboflavin	4 γ/gm. creatinine

With parenteral vitamin B complex therapy, vision in both eyes was 20/20 by July 6, 1951, with both corneas cleared of epithelial changes.

CASE 10.—F. A. (Aug. 2, 1951), a 27-year-old married woman, had had foggy vision for three weeks and was breast feeding a 1-year-old child. She had angular stomatitis and numbness of the extremities. Both eyes showed dystrophy of the corneal epithelium, with the following distribution:

Right Left

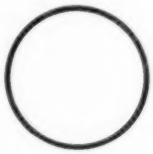
Vision was less than 20/200 on the right and 20/120 on the left. There was a large centrocecal scotoma for form on the right and a central scotoma, also for form, on the left. A diagnosis of nutritional corneal epithelial dystrophy and nutritional retrobulbar neuropathy, bilateral, was made.

Biochemical Examinations

Vitamin A blood level	12 γ/100 ml.
Carotene blood level	57 γ/100 ml.
Urinary excretion for thiamine	24 γ/gm. creatinine
Urinary excretion for riboflavin (result considered invalid owing to an inadvertent error in the technique of examination)	

With the administration of vitamin B complex intramuscularly, by Aug. 14 the dystrophy was reduced and vision was improved to 20/120 on the right and 20/60 on the left. By Aug. 24 there was no longer any corneal dystrophy, and vision for the right and left eyes was 20/60 and 20/40, respectively, with a very much reduced central scotoma for form still present. Further follow-up of the case is lacking.

CASE 11.—F. Z. (Oct. 15, 1951), a 32-year-old married woman, had had foggy vision since her seventh month of pregnancy and was breast feeding a 1-month-old child. She had angular stomatitis. The cornea was clear on the right, but that on the left had corneal epithelial dystrophy, with this distribution:



Right (clear)

Left

There was a central scotoma for form in both central fields of vision. V.O.D. was 20/60, and V.O.S. was 20/200.

Biochemical Examinations

Vitamin A blood level	25 γ/100 ml.
Carotene blood level	23 γ/100 ml.
Urinary excretion of thiamine	103 γ/gm. creatinine
Urinary excretion of riboflavin	162 γ/gm. creatinine

With parenteral administration of vitamin B complex, by Oct. 26 vision was 20/40 on the right and 20/120 on the left, with a remarkable reduction in the amount of corneal dystrophy. By Nov. 3 vision was 20/30 on the right and 20/60 on the left, with no more corneal stipplings but with a small central scotoma on the right and a slightly larger one on the left.

CASE 12.—I. A. (Oct. 22, 1951), a 28-year-old married woman, had had foggy vision intermittently since April, 1949, when after delivery and while breast feeding, she came to this clinic with a condition which was there diagnosed as nutritional corneal epithelial dystrophy. She recovered then with parenteral vitamin B complex therapy, but a year later, after a second delivery, the same condition again developed. The dystrophic changes in the cornea at that time were more intense and appeared almost like a sheet of grayish opacity involving the epithelial layer, Bowman's membrane, and part of the substantia propria of the cornea. With vitamin B complex, vision could be improved only to 20/120 in both eyes, with a residual opacity of the anterior third of the cornea. The present recurrence appeared as a worsening of her already impaired vision after a third delivery and while breast feeding, four months before. Both corneas showed the same sheet-like epithelial opacity, with loss of Bowman's membrane and thinning of the substantia propria. She had peripheral polyneuropathy. The blood Kahn test was negative. She was given a diagnosis of nutritional corneal epithelial dystrophy with irreversible tissue changes. Vision on the right was less than 20/200, while that on the left was 20/200.

Biochemical Examinations

Vitamin A blood level	51 γ/100 ml.
Carotene blood level	47 γ/100 ml.
Urinary excretion of thiamine	75.26 γ/gm. creatinine
Urinary excretion of riboflavin	53.89 γ/gm. creatinine

With parenteral B complex vitamin therapy, vision again improved, but only to 20/120 in each eye.

CASE 13.—P. C. (June 19, 1952), an 18-year-old married woman, had had foggy vision for four months, following delivery and breast feeding. Vision had progressively become worse

the last few weeks. Cheilosis had been present the last month, and numbness and paraesthesias of the extremities of the glove-and-sock type, the past two weeks. Both corneas showed dystrophy of the corneal epithelium, with the following distribution:

Right Left

V.O.D. was 15/100, and V.O.S. was less than 20/200. There was bilateral central scotoma for form. A diagnosis of nutritional dystrophy of the corneal epithelium and nutritional retrobulbar optic neuropathy, bilateral, was given.

Biochemical Examinations

Vitamin A blood level	32 γ/100 ml.
Carotene blood level	117 γ/100 ml.
Urinary excretion of thiamine	18.67 γ/gm. creatinine
Urinary excretion of riboflavin	89.72 γ/gm. creatinine

Parenteral vitamin B complex therapy was started. By July 4, 1952, the corneas were both clear, and vision was 20/30 — in the right eye and 20/40 — in the left eye. The central scotoma on the right was then only for red and blue, but that on the left was still for form, though much smaller. By July 18 vision had become 20/20 for both eyes, with the dystrophic changes of the corneae and the scotoma no longer present.

COMMENT

On the basis of studies and the results set forth in the preliminary report, the term "nutritional dystrophy of the corneal epithelium" was applied to lesions which had the following physical characteristics:

1. They appear as grayish superficial punctate opacities giving a stippled effect to the surface of the cornea, with the individual lesions varying in size from barely perceptible to confluent pinhead-sized or larger.

2. They are as a rule grouped closely at the pupillary area with a predilection for involving the lower half more than the upper, with sparing of the periphery and the limbus.

3. By biomicroscopy, the early lesions are confined to the corneal epithelial layer alone, appearing as highly refractile nodules slightly elevated over the epithelial surface. In advanced cases with permanent or irreversible changes, there are a sheet-like thickening of the epithelium, disappearance of Bowman's membrane, and thinning of the substantia propria.

These lesions also have the following other attributes:

1. They appear frequently associated with signs and symptoms now considered indicative of deficiency in vitamins, particularly of the B complex group, such as angular stomatitis and peripheral polyneuropathy.

2. They have not been observed in children and have higher incidence in the age group between 21 and 40 years.

3. They are related to, or are frequently associated with, pregnancy and breast feeding, an association which may in part explain why there is a higher incidence in females and in the age group of 21 to 40 years, and with chronic food deprivation and chronic illnesses.

4. They undergo rapid resolution with parenteral administration of vitamin B complex, provided this is given early enough and before irreversible changes, with involvement beyond Bowman's membrane, have taken place.

The association of these lesions with other signs and symptoms indicative of deficiency in the vitamin B complex group, and the very favorable effects of the administration of the B complex vitamins on these lesions in themselves strongly suggest deficiency in this group of vitamins as an important causative factor. Nevertheless, it concerns us at this time to determine the vitamin state of the patients showing these lesions by more direct means. For this, quantitative biochemical examinations of the patients for vitamin A, carotene, thiamine, and riboflavin were resorted to.

Vitamin A and carotene levels in the blood were determined in the Philippines Institute of Nutrition by the micromethod of Bessey, Lowry, Brock, and Lopez.[2] Thiamine in the urine was measured by the thiochrome technique described by Mickelsen, Condiff, and Keys,[3] while riboflavin, also of the urine, was measured by direct reading of fluorescence of urine after an acidified urine sample had been freed of interfering materials by oxidation with potassium permanganate.

The standards for the normal with which we have compared the findings in our cases are United States standards,* in lieu of similar standards for Filipinos. These are as follows:

*United States Standard Normal Values for Vitamin A and Carotene**

	Poor	Fair	Good	Excellent
Blood vitamin A, γ/100 ml	Below 20	20 to 29	30 to 49	Above 50
Blood carotene, γ/100 ml	Below 75	75 to 124	125 to 199	Above 200

* After Bessey, Lowry and others.[2]

Thiamine excretion by normal subjects receiving adequate amounts of thiamine ranges from 150 to 300 γ per gram of creatinine (Adamson and associates[4]). Burch and associates,[5] in nonsymptomatic Filipinos in the Bataan Nutritional Survey, observed an average urinary excretion of 71.4 γ per gram of creatinine, which is below the normal United States standards but which supports the findings of Williams and associates[6] that symptoms of thiamine deficiency do not appear unless urinary excretion falls below 50 γ per gram of creatinine.

On the basis on the above standards, three of our subjects (23.07%) had poor vitamin A levels in the blood, one (7.69%) had a fair level, six (46.15%) had good levels, and three (23.07%) had excellent levels. Carotene blood levels in all the 13 subjects were below 75 γ per 100 cc., and so were to be regarded as poor. The average blood level of vitamin A for the group was 25.5 γ per 100 cc., which is fair; that of carotene was poor, indicating insufficient day-to-day dietary intake of vitamin A precursors.

* After Bessey, Lowry, and others.[2]

On the other hand, thiamine excretion in the urine in 10 of our cases was very low, ranging from 9 to 75 γ per gram of creatinine. In only two cases (Cases 8, with 125 γ, and Case 11, with 103 γ) did the excretion exceed 100 γ per gram of creatinine, but even then it was still below the lowest normal level, of 150 γ per gram of creatinine, as set by Adamson.

Riboflavin excretion in the urine was even lower, for while the normal range is from 500 to 800 γ per gram of creatinine, the average for the group was only 47.8 γ per gram of creatinine.

In this connection, it may be pertinent to explain that we have used the thiamine and riboflavin excretion in the urine as a means of evaluating the vitamin B complex status of the cases because the blood determination is more difficult. In the first place, there is hardly any free thiamine in the blood plasma (Hennesey[7]), thiamine being found in the body almost entirely as "bound" thiamine in cells, so that a blood thiamine determination means the thiamine determination of the cellular contents of the blood; in the second place, Burch[5] has found that there are only small decrements in blood thiamine with increasing severity of beriberi symptoms, and that the differences between the two groups, one of nonsymptomatic cases and the other of frank cases, are not statistically significant. Melnick,[8] in comparing the results of urinary thiamine values and the estimation of vitamin stores in the body with tests related to carbohydrate metabolism, considers the urinary thiamine values as the more sensitive.

The biochemical findings in these cases confirm the impression that lesions of the corneal epithelium of this type appear in persons with marked deficiency in the B complex group of vitamins, particularly thiamine and riboflavin, an observation which explains the rapid favorable response of these lesions to the correction of the deficiency.

Of course, there may be other contributing etiological factors, which are hard to evaluate. By this, I refer to the factor of tissue resistance, which may explain why dystrophic lesions of the corneal epithelium do not appear in all cases of hypovitaminosis of the B complex, or to the factor of possible minimal trauma to the corneal epithelium, which under normal conditions of nutrition would not have had any effects on it. However, fundamentally, the cause remains unchanged—a deficiency in the B complex group of vitamins.

In countries and places in which the problem of nutrition exists, and there are many such places, there also exist ocular diseases which are directly related to deficiencies in various elements of nutrition. Many of these diseases we may now know, but how many more of these we still have to recognize is a question that only much study in the locality of their existence can answer.

SUMMARY

A total of 13 cases of nutritional dystrophy of the corneal epithelium is presented, together with results of their biochemical blood and urinary vitamin determinations.

The group as a whole showed a fair amount of vitamin A storage in the body, despite a low carotene intake, and a very low dietary intake and storage of thiamine and riboflavin. These findings, added to the rapid resolution of the early lesions with

the administration of vitamin B complex, strongly support the concept of vitamin B complex deficiency as the basic factor in the production of these changes in the corneal epithelium.

Dr. Juan Salcedo Jr., Secretary of Health and chief of offices of the Institute of Nutrition, Philippines, and Dr. Arsenio Regala, medical nutritionist, afforded me the facilities of the Institute, and Mrs. Carmen Llamas-Intengan, biochemist of the Institute, performed the quantitative biochemical blood and urinary examinations.

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THREE NEW CYCLOPLEGIC DRUGS

Clinical Report

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OF A GROUP of new parasympathomimetic-blocking agents, three appear to be effective cycloplegic drugs suitable for refraction. These compounds are esters of disubstituted acetic acids (Treves and Testa *; Ehrenberg, Ramp, Blanchard, and Treves †). These drugs have been reported as cyclopentolate ‡ (Compound 75 GT), Compound 92 GT and Compound 93 GT. Their usage in 0.5% solution has been previously reported (cyclopentolate, by Priestley and Medine,[2] and all three compounds by Gettes and Leopold [3] and by Stolzer [4]). Their cycloplegic efficiency appeared greater than that of homatropine but not quite as great as that of atropine. In addition, they possess the advantage of a shorter duration of activity and an absence of local or systemic reactions. This report concerns the study of the effect of 1% solutions of the same preparations.

TABLE 1.—*Cycloplegic Activity of Cyclopentolate and Compounds 92 and 93 GT*

Drug Used	No. of Patients *	No. of Failures	Percentage of Failures
1% cyclopentolate	213	9	4.2
1% Compound 92 GT	150	4	2.7
1% Compound 93 GT	157	5	3.1

* All patients were Negroes.

Two per cent solutions were also employed, but in this concentration these compounds were found to produce excessive conjunctival irritation, with subjective burning and marked conjunctival hyperemia.

In view of previous experiences with parasympathomimetic-blocking agents, Negro patients were used for refraction because in general their irides were found to be somewhat refractory to cycloplegic drugs. In testing or comparing newer agents of this type, eyes with pupils which are ordinarily most difficult to dilate

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* Treves and Testa.[1] Personal communication to the author.

† Ehrenberg, M. H.; Ramp, J. A.; Blanchard, E. W., and Treves, G. R.: Antispasmodic Activity of Basic Esters and Quaternary Derivatives of B-Hydroxy Acids, personal communication to the authors.

‡ Cyclopentolate (Compound 75 GT) is marketed under the trade name Cyclogyl by Schieffelin & Company, New York.

should be utilized, rather than lightly pigmented, blue irides, which appear to dilate very readily and in which profound cycloplegia can be produced with even weak solutions of cycloplegic drugs.

All the solutions were in a concentration of 1.0% in a boric acid-borate buffer of approximately pH 5.7, with 1:50,000 benzalkonium chloride added as a preservative.

The drops were used as follows: One drop of the solution tested was instilled into each eye; the instillation was repeated in five minutes. The patients were examined one hour after the last instillation. The amount of residual accommodation was then measured and compared with previously reported experiences. The cycloplegic was considered as ineffectual if 2.5 D. or more of residual accommodation was present. In addition to their use in these 520 Negro patients, these three preparations were employed in the examination of 469 white patients. One drop was instilled in each eye of the white patients, and the examination was performed within one hour. The residual accommodation was measured in these 469 patients, as was previously described (Gettes and Leopold [3]).

One hundred fifty patients were examined with 1% cyclopentolate. Of this group, only one patient had incomplete cycloplegia, i. e., a residual accommodation of 3.0 D. in each eye.

One hundred fifty patients were examined with 1% Compound 92 GT and 169 with 1% Compound 93 GT, and in all these white patients the residual accommodation was less than 2.0 D.

Four white, blue-eyed, blond children, who had previously exhibited toxic systemic reactions to atropine, had refraction with 1% cyclopentolate. These four patients were 5, 6, 11, and 13 years of age, respectively.

If these results are added to Table 2 in the previous report (Gettes and Leopold[3]), they will read as follows:

TABLE 2.—*Effectivity of Cycloplegics in Patients with Dark Irides and Darkly Pigmented Skin*

Drug	Effectivity, % *
4% homatropine in 1% hydroxyamphetamine (Paredrine) HCl	54
0.5% cyclopentolate (Compound 75 GT)	66
0.5% Compound 92 GT	75
2% homatropine with 2.5% dibutoline sulfate	76
0.5% Compound 93 GT	79
1% cyclopentolate	96
1% Compound 93 GT	96.7
1% Compound 92 GT	97.3
1% atropine	100

* Percentages are based on having residual accommodation of 2.5% D. or less.

Compound 93 GT caused lacrimation, redness, and burning in almost 50% of the patients. Although no staining lesions of the cornea were noted, none of the patients tested manifested any local or systemic toxic reactions. The 1% solutions of cyclopentolate and Compound 92 GT were found to be nonirritating and produced no subjective complaints of burning, itching, or tearing.

Twenty-five patients who had been examined with each drug were reexamined after 24 hours, and all of them were able to read. Significantly, however, mydriasis persisted in 40% of all these patients for approximately 24-36 hours.

Since then, these drugs have been used routinely in my private practice. Most of these patients have been of the Caucasian race and had previously had refraction with either 1% atropine solution for three days or 4% homatropine-1% hydroxyamphetamine hydrochloride solution.

One instillation of cyclopentolate was sufficient for refraction in patients over 16 years of age. In only four white patients was it necessary to instill a second drop of the solution. This procedure should be followed if mydriasis is not apparent within 20 minutes.

The 1% solution of Compound 92 GT or Compound 93 GT was instilled twice in the younger age group, who previously had been examined with atropine (0.5 or 1% used for three days. All the patients in this group of private patients had not more than 2.00 D. of residual accommodation.

In adults, as well as in children, cycloplegia was adequate within one hour. These patients exhibited as much or more hyperopia as when previously examined with 4% homatropine hydrobromide in 1% hydroxyamphetamine hydrochloride. Those having refraction with Compound 92 GT revealed essentially the same cycloplegic findings as had been determined when previously examined with atropine (0.5 or 1%) for three days. Because of the more frequently reported subjective discomfort with Compound 93 GT, use of this drug has been discontinued for refraction, but it is of value as a therapeutic agent.

To 100 white patients (adults) tested with 1% cyclopentolate, 0.25% physostigmine salicylate solution was instilled at the completion of their examination. All but six patients were able to read eight hours later.

Of the 100 private patients tested with 1% Compound 92 GT, all but 4 patients were able to read eight hours after the instillation of the 0.25% physostigmine solution.

In subsequent patients in whom no counteracting miotic was used, the cycloplegic effect persisted for about 12 hours.

In approximately 40% of all patients tested, mydriasis persisted after 24 hours, even though no cycloplegia was present.

Tactile tensions noted on all patients showed no apparent rise in intraocular tension after the use of these drugs. To date, no patient has exhibited any local or systemic toxic reaction.

As a result of this study, these preparations are now being employed routinely in the clinic of the Wills Eye Hospital and in my private practice. To date, these drugs have been used in a total of over 3,000 patients with no apparent local or systemic toxic reactions.

EFFECT ON PATIENTS SENSITIVE TO ATROPINE

Twenty patients who exhibited local conjunctivitis and/or a contact dermatitis of the skin of the eyelids following prolonged use of atropine were treated interchangeably with 1% cyclopentolate, Compound 92 GT and Compound 93 GT. Of these, two were private patients who exhibited their atropine sensitivity during their postoperative care following retinal detachment surgery. One of the detached retina patients was a Negro who was also sensitive to scopolamine. In both instances full mydriasis was maintained for a period of four weeks. Two were postoperative cataract patients, and four were treated for various types of keratitis. The remaining 12 were from the wards of the Wills Eye Hospital.

In severe cases of iridocyclitis or uveitis, it is necessary to employ these drugs every three hours. These preparations have been used as drops and as subconjunctival pledgets. To date, they have not been injected subconjunctivally.

RECOMMENDED METHOD OF USE

1. *Refraction.*—A. In white patients between the ages of 6 and 16 years, 1 drop of cyclopentolate or Compound 92 GT is instilled in each eye; the instillation is repeated in five minutes. The patient is ready for retinoscopy after one hour.

B. In patients more than 16 years of age, 1 drop of cyclopentolate or Compound 92 GT is instilled. The instillation is repeated if no mydriasis is observed in 20 minutes, and examination is done in one hour.

C. In Negro patients (adults) 1 drop of cyclopentolate or Compound 92 GT is instilled in each eye; the instillation is repeated in five minutes and examination done one hour after the last instillation.

D. In Negro children, since insufficient work has been done in this group with these drugs, it is suggested that the use of atropine sulfate be continued—1 drop three times a day for three days prior to examination.

2. *Treatment and Postoperative Care.*—Drops are used every three or four hours when one of these drugs is substituted for atropine in inflammatory cases. These drugs may be utilized wherever homatropine or scopolamine is indicated.

To obtain full mydriasis prior to cataract surgery, these drugs are adequate. Cyclopentolate and Compound 92 GT were each employed preoperatively in six patients and found to be effective. One drop was instilled 1 hour prior to surgery, with a second instillation 30 minutes preoperatively.

CONCLUSIONS

One per cent solutions of cyclopentolate and Compounds 92 GT and 93 GT appear to be superior to our present shorter-acting cycloplegic drugs.

1. They appear to leave, at the most, as little residual accommodation as atropine.
2. Their cycloplegic effect is of short duration, shorter than that of homatropine or atropine. The patients can work or read the following day. Moreover, children of school age can resume their school work the following day.

Thus, the chief handicap of maximum cycloplegia, namely, its incapacitating effect, is minimized with these newer drugs. Patients can thus be assured that, except for the day of their examination, no time will be lost from work.

3. The drugs appear to be safe and can be employed wherever one would ordinarily use a cycloplegic. Of these GT compounds, only Compound 93 GT appears to be irritating subjectively.
4. These drugs do not produce any local or systemic toxic effects.

In view of the not infrequent systemic toxic reactions seen after the use of atropine for refraction, and in view of the frequent local toxic effects of atropine after its prolonged use in treatment, atropine should eventually be replaced by these efficacious, shorter-acting parasympathomimetic-blocking agents.

Atropine should be employed for refraction only in the children of preschool age with some existing or suspicious muscle anomaly or imbalance.

1930 Chestnut St. (3).

ABSTRACT OF DISCUSSION

DR. IRVING H. LEOPOLD, Philadelphia: Dr. Gettes has obviously performed a great deal of work with these new cycloplegic agents. He has shown that in 0.5% concentration they have a greater cycloplegic efficiency than 4% homatropine. Their cycloplegic effect wears off more rapidly than that of homatropine, and they produce a minimum of local irritability. The results are similar to those that have been reported by Priestley and Medine, Stolzer, and others.

The ideal cycloplegic agent would appear to be one that would have rapid action, whose action would persist only long enough for a careful refraction to be performed, that would have no local or systemic toxic features, and whose effects, if possible, could be dissociated from the mydriasis. The drugs studied by Dr. Gettes are not ideal cycloplegic agents, but they do approach the ideal that has been postulated.

Within the past few years a number of new compounds have been investigated as substitutes for homatropine or atropine. Dr. Swan introduced dibutoline sulfate. The British workers have produced a compound called E-3, or Lachesine, which was recently reported upon in this country by Feldman. Kiess and Fralick have worked with Blicke's compound, and Drucker and Cazort, with Compound BL-139. These are all anticholinergic agents, which can be used as substitutes for homatropine, and have a varying degree of potency.

It is interesting to note the ease with which these GT compounds can be overcome by the use of physostigmine or pilocarpine. This suggests that their cycloplegic effect, their anticholinergic blocking action, is a rather weak one; therefore, as Dr. Gettes has pointed out, if one is going to use these agents as substitutes for atropine to produce mydriasis, they will have to be administered very frequently.

In all the reports to date there has been no mention of a rise in intraocular pressure following the use of these agents. These have all been employed apparently in normal eyes, and one wonders what the results would be in normal eyes with narrow angles.

We should all be indebted to Dr. Gettes for his conscientious screening of the new cycloplegic agents and of the new anticholinergic agents, in a constant effort to uncover a better drug for cycloplegic and dilatation purposes.

Dr. Isaac S. Tassman, Philadelphia: Dr. Leopold introduced the question of the effect on the intraocular pressure. I was prepared to ask that question first—whether any studies have been made in regard to the effect on the intraocular pressure in the use of these drugs, particularly since they are recommended to replace atropine in the case of adults when the patient might be sensitive to that drug.

For about 15 years my colleagues and I have been using, with complete satisfaction, a mixture of 4% homatropine hydrobromide with 1% solution of hydroxyamphetamine (Paredrine) hydrobromide, instilling 2 drops into the eye for the purpose of cycloplegia. Studies originally made of the effect on the intraocular pressure showed that there was no increase in pressure from the use of this cycloplegic.

There is one statement in the author's results that I should like to call attention to and disagree with, that is that this cycloplegic was found to be only about 54% effective. In our hands the effectiveness of 4% homatropine mixed with 1% hydroxyamphetamine hydrobromide, even in the Negroes, has been 90% at least.

Dr. Bernard C. Gettes, Philadelphia: No tension studies were done with the tonometer. This evaluation is indicated.

Concerning homatropine and hydroxyamphetamine, the figures presented were based upon actual measurements of residual accommodation, and not simply on giving the patient a chart to read and asking, "Can you or can you not read it?"

In testing drugs of this nature, some uniformity must be obtained in measuring the residual accommodation. This was brought out very clearly in an article by Brickley and Ogle (*Am. J. Ophth.* **36**:649 [May] 1953) in which the variation in the amounts of residual accommodation with different methods and different examiners is shown.

Our figure of 2.5 D. is based on our particular method of measuring residual accommodation. Even with atropine, a few patients had 2.00 and 2.25 D., which corresponds to the figures obtained by Dr. Prangen in his report of what constitutes satisfactory cycloplegia.

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VARIOUS ANESTHETIC AGENTS USED IN RETROBULBAR INJECTIONS

A Comparative Study

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RETROBULBAR anesthesia was first described by Pooley [1] in 1914, but there are still many misconceptions concerning its mode of action and there is considerable disagreement about indications for its use in surgery of the eye. Spaeth,[2] in his textbook on ophthalmic surgery, stated that the danger from forcible contraction of the four rectus muscles is greater than from squeezing of the orbicularis oculi muscle in intraocular surgery. He said, however, that it is not wise to use a retrobulbar anesthesia in a prominent eye. Kirby [3] described a proptosis after injection of 1 cc. of procaine hydrochloride, which he said may have been due to hemorrhage or may have been the result of a transudation producing edema of the orbital tissues; he, therefore, used retrobulbar anesthesia in selected cases only but made no mention of what his criteria were. Elschnig [4] mentioned that there resulted some loss of movement of the globe in all directions and that reflex contraction of the extraocular muscles was impossible. He pointed out that there is a reduction of tension, starting in 8 to 10 minutes, which may become so marked as to interfere with the technique but that, along with this, the vitreous pressure is reduced. Icaza [5] used 1 cc. of 2% procaine hydrochloride with 0.1 cc. of 1 : 1,000 epinephrine hydrochloride, which caused complete anesthesia of the globe and "adnexa," rapid and complete pupillary dilatation, and a noticeable lessening of the intraocular tension. He observed that the eye occasionally becomes softer than is desirable, since he felt that the technique of a cataract extraction is made more difficult with too soft an eye.

Atkinson,[6] in a fine article, described his technique for retrobulbar anesthesia. He uses only 1 to 1.5 cc. of solution because he feels that more might cause proptosis; such amounts result in a blocking of sensory nerves to the globe and of sensory and motor nerves to the extraocular muscles. He stated that there is a definite decrease in intraocular tension after an injection within the cone, and that this decrease is greater if the amount of epinephrine is increased to 3 or more drops per 5 cc. of solution. He explained the drop in pressure as the result of the constricting action of epinephrine on the arteries entering the globe, so that there is a decreased blood inflow; however, since the solution containing the epinephrine does not reach the

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venae vorticosae, the outflow of blood is not impeded. Additional effects of the retrobulbar anesthesia are a noticeable deepening of the anterior chamber and, by inference, a proptosis, this proptosis being of help in deep-set eyes. His indications for retrobulbar injection are all operations on the globe, extraocular muscle operations, enucleation, evisceration, and cases of acute glaucoma for immediate relief of pain.

In a later article, Atkinson [7] discussed the use of hyaluronidase added to the retrobulbar injection (6 turbidity-reducing units per 1 cc.) and pointed out that a temporary paralysis of the extraocular muscles could be achieved with a greater degree of success with this substance. In addition, he emphasized the fact that hypotony is more pronounced when hyaluronidase is added to the procaine, resulting in a slower and technically more difficult extraction, but one in which there is less danger of vitreous loss. The cause of this hypotony he postulated as being due to one of three factors: (*a*) a greater relaxation of the extraocular muscles; (*b*) a more extensive constriction of the arteries entering the globe, or (*c*) a depolymerization and hydrolysis of the hyaluronic acid in the vitreous, causing water to be released.

Scheie and Ojers,[8] working with dogs, stated that a retrobulbar injection of procaine produces an effect exactly similar to that achieved by ciliary ganglionectomy and that with a well-placed injection there is pupillary dilatation within 30 to 60 seconds. They maintained that failure to achieve such pupillary dilatation is the result of a misplaced injection and that, if the animal is injected the second time in the proper place, prompt dilatation results.

Gifford,[9] after extensive anatomical studies, felt that a more complete paralysis of the extraocular muscles could be obtained by injecting the anesthetic solution at the apex of the orbit rather than in the muscle cone immediately posterior to the globe. This he felt was very important, since he ascribed a large percentage of vitreous loss to contractions of the extraocular muscles. In addition, as side-effects he mentioned a pupillary dilatation and a decrease in intraocular tension after such a procedure. Dr. Edward Burch, in his discussion of this paper, pointed out the desirability of further control studies and a more accurate comparison of the results achieved by ordinary techniques of injecting retrobulbar anesthesia with the "floating" technique described by Gifford.

In a second article, Gifford [10] surmised that some of the tension-lowering effect of a retrobulbar injection may be produced by block of the ciliary nerves but that further effect comes from the motor block. He checked the effect of epinephrine alone and procaine alone and found that it was not necessary to include the former in the solution to achieve a lowering of tension. He concluded that the procaine must produce its tension-lowering effect by blocking the parasympathetic activity of the third nerve and the ciliary ganglion.

Recently a new agent, lidocaine (Xylocaine), has become commercially available, but as yet there are no detailed reports of its effectiveness when injected retrobulbarly. It is unique in that one of its inherent properties is an ability to diffuse through the tissue. In this regard it is supposed to be about as effective as procaine of twice the strength to which hyaluronidase has been added. Epinephrine, which may or may not be added to the solution, increases the period of its effectiveness.

From the foregoing it is clear that further information concerning the effects of retrobulbar anesthesia is necessary in order to establish more clearly both its indications and the best techniques for its use. With this in mind, a problem was set up which would compare Gifford's "floating" technique with the more usual technique and would also compare the effects of procaine, epinephrine, and hyaluronidase singly and in combination, and lidocaine. Patients at the Illinois Eye and Ear Infirmary of the University of Illinois who were to have surgery the next day were examined. Care was always taken to select only patients with uncomplicated lens opacities. From a clinical standpoint it was felt that much information could be obtained by observing the effect of a retrobulbar injection on (1) the relative prominence of the globe, (2) the intraocular tension, (3) the pupillary size, (4) the extraocular muscles, (5) the depth of the anterior chamber, and (6) the corneal sensitivity.

MATERIALS AND METHODS

The following solutions were employed in various combinations: procaine hydrochloride, 2%; epinephrine, 1:50,000; hyaluronidase, 7.5 turbidity-reducing units per 1 cc.; lidocaine hydrochloride, 1%, and isotonic saline.

It was originally proposed to compare Gifford's "floating" technique[9] of injecting the anesthetic solution at the apex of the orbit with the more usual method of injection into the muscle cone immediately posterior to the globe. The Gifford method, employed with the first six patients, resulted in two retrobulbar hemorrhages. Although this high incidence may have been the result of faulty technique, prudence dictated that the method be abandoned. Subsequently the technique described by Atkinson[6] was employed, in which a 3.5 cm. 25-gauge needle is introduced through the skin of the lower lid in a direction up and nasally to pass between the inferior and the lateral rectus muscle. The injection of 1.5 cc. of solution into the muscle cone is facilitated by having the patient look up and nasally. This was more easily accomplished in prominent eyes and required shallower injection. In contradistinction to the experience with the Gifford technique, only one retrobulbar hemorrhage was encountered in 97 injections.

Prominence of the globe was measured prior to the injection and within five minutes afterward by means of a Hertel exophthalmometer. Tensions were taken with the Schiøtz tonometer before injecting and 5, 10, 30, and 60 minutes thereafter. The pupillary size was estimated by means of a millimeter rule under standard lighting conditions before and at intervals after the injection. Function of the extraocular muscles was estimated by observing ductions, and Gifford's method of scoring the percentage of muscles paralyzed was used. With this method, 100% is scored if all six muscles are paralyzed, each rectus counting 20% and each oblique counting 10.%. Corneal sensitivity was determined roughly by using a wisp of cotton. Since it was necessary to instill a drop of butacaine sulfate 2% to take the initial tension, subsequent testing of corneal sensitivity was done by comparing how much longer tonometry could be done on the eye being tested than on the fellow eye, which had had a drop of butacaine only.

RESULTS

1. *Effect on Prominence of the Globe.*—In 10 cases the prominence of the globe was measured with the Hertel exophthalmometer both prior to injection and within five minutes after injection. In six cases there was no change in the measurement; in one case the globe was more prominent after injection by 1 mm.; in two cases, by 2 mm., and in one case, by 3 mm. In view of the fact that measurements with the Hertel exophthalmometer were not accurate to within 2 mm. in our hands, it was concluded that clinically the injection of these amounts of solution caused no significant increase in the prominence of the globe.

2. *Effect on Ocular Tension.*—Neither epinephrine, hyaluronidase, nor saline caused any change in the intraocular tension. On the other hand, any solution con-

taining procaine or lidocaine was capable of producing a drop in the tension (Chart 1 and Table). This drop was greatest between 5 and 10 minutes after the injection, and after 30 minutes there was a definite tendency to recover. After 60 minutes this tendency toward recovery continued but was less marked in those cases in which epinephrine or epinephrine and hyaluronidase had been added to the procaine.

The Table shows that with 2% procaine alone there was an average drop of 2.2 mm. in 27 cases. In one case in which procaine alone was used, there was a drop in intraocular pressure of 8 mm., and in nine cases there was a drop of 4 mm. or

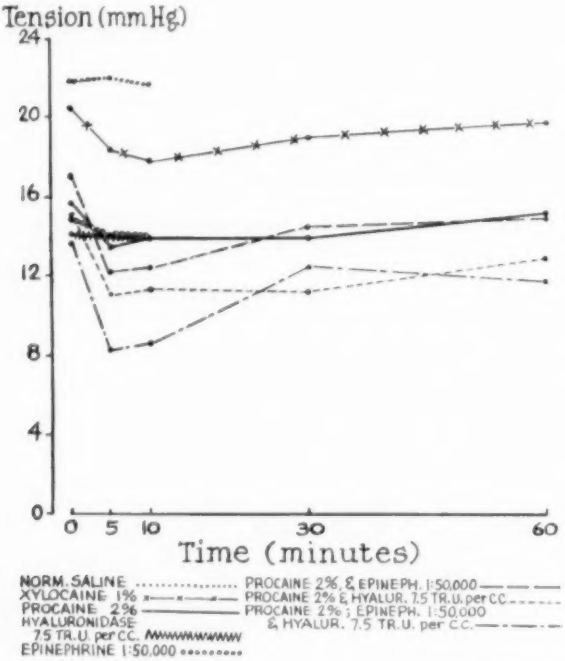

Chart 1.—Effect of retrobulbar injections on ocular pressure.

Effect of Retrobulbar Injections on Ocular Tension

Solution	No. of Cases	Average Initial Tension*	Average Reduction in Tension After 5 Min.*	Standard Error
Procaine HCl 2%	27	15.9	2.2	0.5
Procaine 2%-epinephrine 1:50,000-hyaluronidase 7.5 T. R. U.	10	13.8	5.9	0.9
Procaine HCl 2%-epinephrine 1:50,000	10	17.1	4.8	0.7
Procaine HCl 2%-hyaluronidase 7.5 T. R. U.	10	14.8	3.6	0.6
Lidocaine 1%	10	20.4	2.1	0.6
Hyaluronidase 7.5 T. R. U. only	10	14.1	0.1	0.4
Epinephrine 1:50,000 only	10	14.7	0.5	0.03
Isotonic saline only	10	21.9	0.3	0.1

* Measured in millimeters of Hg (Schiøtz).

more. In 12 cases with procaine alone, there was a change of only ± 1 mm. Clinically, it seemed that the greatest decrease in intraocular tension generally occurred in those cases with the most effective retrobulbar anesthesia in the sense that more extraocular muscles were paralyzed, that the pupils were more widely dilated, and that corneal anesthesia persisted longer. There were five cases, however, with a decided drop in tension in which only one or two muscles were paralyzed. It seemed that if the procaine had been injected at just the right spot, a drop in the intraocular pressure resulted.

Addition of epinephrine or hyaluronidase or both to the procaine produced a greater average drop in pressure in the 10 cases in which each combination was used than in the cases in which procaine alone was used. In each series there were some

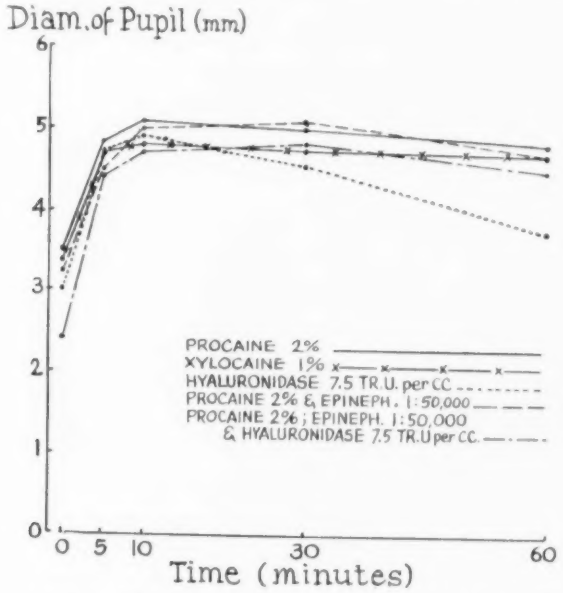

Chart 2.—Effect of retrobulbar injections on pupillary size.

instances in which the retrobulbar injection had no effect on the tension. In all cases the maximum drop in pressure occurred within five minutes (Chart 1), and recovery was complete or nearly complete in one hour. It can be assumed that the addition of hyaluronidase or epinephrine or both enhances the anesthetic effect or allows the anesthetic solution to reach the proper site of action in a greater number of cases.

Lidocaine had the same effect as procaine alone, producing the same average decrease in intraocular tension at the end of five minutes. The duration of its effect was similar also to those solutions containing procaine.

These experiments do not support the clinical impression of many surgeons that a retrobulbar injection of procaine, epinephrine, and hyaluronidase produces a much softer eye than one of procaine and epinephrine alone.

3. *Effect on Pupillary Size.*—Pupillary dilatation occurred within five minutes after retrobulbar injection of lidocaine or any solution containing procaine, except in a few cases in which the pupil had been dilated maximally by a mydriatic previously. Injection of isotonic saline, epinephrine, or hyaluronidase alone or in combination and without procaine had no effect on the size of the pupil. Pupils dilated by the retrobulbar anesthesia did not react to light, a finding which was taken to indicate a definite response, even though the pupillary dilatation was not wide. An interesting observation was that one patient who had been on 1.5% carbachol (Carcholin) four times daily showed no dilatation of the pupil after an injection of 2% procaine, even though there was a reduction of the tension and paralysis of four of the extraocular muscles to indicate an otherwise successful retrobulbar anesthesia.

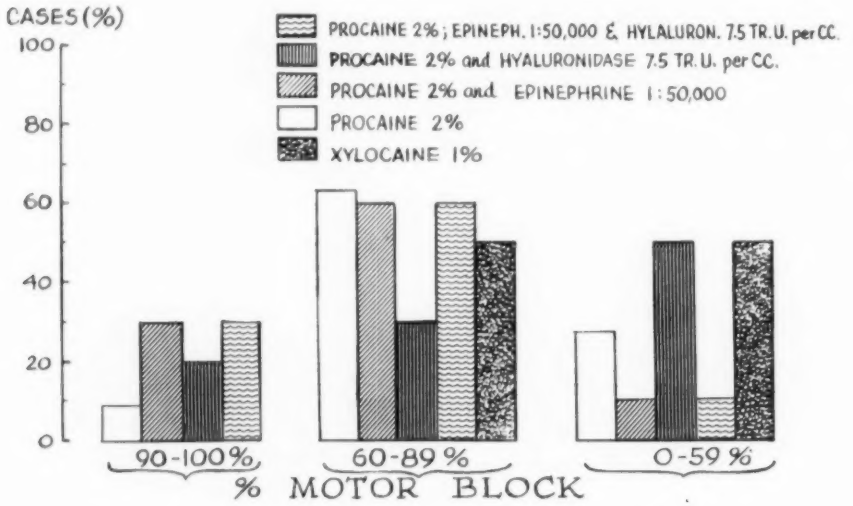

Chart 3.—Paralyses of the extraocular muscles following retrobulbar injection.

4. *Effect on the Extraocular Muscles* (Chart 3).—Epinephrine, hyaluronidase, and saline alone or in combination had no effect on the extraocular muscles in any case. Solutions containing procaine or lidocaine produced a paralysis of some or all muscles in all cases within 10 minutes. It appeared that procaine-epinephrine and procaine-epinephrine-hyaluronidase had the greatest effect, followed, in decreasing order, by procaine-hyaluronidase, procaine alone, and lidocaine alone. In Gifford's series,[9] an effective motor block of over 60% was obtained in 117 of 158 cases (74%); in our series an effective motor block of 60% or over was obtained in 44 of 62 cases (71%). These figures indicate that in our hands injection by the usual technique is as effective as the deep retrobulbar injection described by Gifford. Certain cases with effective muscle paralysis showed no reduction of tension, while others, with only one or two muscles paralyzed, showed a definite decrease in tension. This would suggest that it is not the paralysis of the extraocular muscles *per se* which is responsible for the reduction of tension.

5. *Effect on the Depth of the Anterior Chamber.*—In the 10 cases which received procaine-epinephrine there was no clinical change in the depth of the anterior chamber as determined by slit-lamp study before and after injection.

6. *Effect on Corneal Sensitivity.*—Estimation of corneal sensitivity following injection was made difficult by the fact that it was necessary to instill a drop of 2% butacaine in order to take an initial tension before the retrobulbar injection was made. It was found that tonometry itself became a good indication of corneal anesthesia; if tonometry was possible on the eye which had received the injection long after it was possible on the fellow eye which had had butacaine only, this was taken as a measure of the effectiveness of the injection in producing corneal anesthesia. Epinephrine, hyaluronidase, and saline produced no corneal anesthesia. Solutions containing procaine or lidocaine produced a corneal anesthesia which lasted at least 30 minutes, and usually 60 minutes. There was no relation between the corneal anesthesia and the effectiveness of the anesthesia as measured by degree of muscle paralysis or decrease in tension.

SUMMARY AND CONCLUSIONS

The effect on the ocular tension, pupillary size, corneal sensitivity, depth of the anterior chamber, prominence of the globe, and extraocular muscles of the retrobulbar injection of isotonic saline, 1% lidocaine (Xylocaine) hydrochloride, and various combinations of 2% procaine hydrochloride, epinephrine, and hyaluronidase solutions has been described. Epinephrine, hyaluronidase, and isotonic saline alone had no effect on any of the matters under consideration. The injection of 1.5 cc. of any given solution did not cause a significant proptosis. There was only 1 retrobulbar hemorrhage in 97 injections. Ocular tension was reduced similarly by 2% procaine and 1% lidocaine. Addition of epinephrine or hyaluronidase to the procaine increased the tension-lowering effect; addition of both produced an even greater effect. Ordinary retrobulbar injections, especially with procaine-epinephrine or procaine-epinephrine-hyaluronidase, seemed to produce akinesia of the extraocular muscles equivalent to the deep retrobulbar injection described by Gifford; 1% lidocaine appeared to be less effective in producing akinesia of the extraocular muscles. No relation was found between the degree of paralysis of the extraocular muscles and the reduction of tension.

The total effect of the retrobulbar injection can be attributed to the nerve block produced. The epinephrine, when added to the procaine, possibly enhances the effect of the latter by causing a more profound nerve block. The addition of hyaluronidase may cause an injection which is wide of the mark to be more effective by its spreading action. In some instances, however, the injection of plain procaine, properly placed, is capable of causing a profound retrobulbar anesthesia as measured by our criteria.

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ISONIAZID IN TUBERCULOUS UVEITIS

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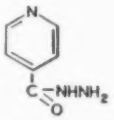
ISONICOTINIC acid hydrazide, now officially designated isoniazid, was first synthesized in Germany in 1912 as an exercise for a degree in chemistry.[1] Prior to the use of this drug in pulmonary tuberculosis no medical or commercial use was known. Isoniazid was one of over 5,000 drugs tested in vitro and in vivo against Mycobacterium tuberculosis at the Squibb Institute for Medical Research. Isoniazid is marketed under many trade names, among which are Nydrazid, Rimifon, Dinacrin, and INH.*

This report is in three parts: (I) attributes of isoniazid; (II) clinical study of isoniazid in tuberculous uveitis; (III) experimental study of the passage of isoniazid across the blood-aqueous barrier of the rabbit.

I. ATTRIBUTES OF ISONIAZID

Chemistry.—Isoniazid is a pure, colorless, synthetic crystalline compound which is very soluble in water. The general formula is $C_6H_7N_3O$ and the structural formula:



The close relationship to nicotinic acid and its isomers is evident.

Pharmacology.—In animals [2] and man,[3] isoniazid is rapidly absorbed from the gastrointestinal tract with a peak plasma level in from one to six hours. No accumulation occurs regardless of route or duration of administration, and excretion is primarily by way of the kidneys and bowel.[3] A biologically active concentration of isoniazid occurs rapidly in the cerebrospinal fluid of patients with tuberculous meningitis on a dosage of 3 mg. per kilogram a day. The spinal fluid of these patients was found to have a concentration of isoniazid 14 to 65 times that necessary completely to inhibit Myco. tuberculosis H37Rv in vitro for a 14-day period. Little evidence for any parasympathetic-blocking type of autonomic activity has been found.[4]

From the Department of Ophthalmology, Indiana University School of Medicine.

Read before the Section on Ophthalmology at the 102nd Annual Meeting of the American Medical Association, New York, June 4, 1953.

* Eli Lilly & Company, Indianapolis, supplied the INH for this study.

Bacteriology and Toxicology.—In Vitro Activity: Isoniazid is as active in vitro against intracellular as against extracellular tubercle bacilli and in this respect is superior to streptomycin.[5] Isoniazid is tuberculostatic,[6] and recent studies by labeling isoniazid with C^{14} indicate that this bacteriostasis is due to the interference of isoniazid, with the formation of an essential metabolite.[7] Only mycobacteria susceptible to isoniazid become radioactive. Isoniazid in vitro is specific against tubercle bacilli in a very low concentration, and increasing the concentration does not increase its effect.† Since streptomycin penetrates the tubercle bacillus with difficulty, increasing the concentration does increase its effect. Isoniazid has only moderate activity against some common fungi and has slight or no activity against other bacteria.[9]

In Vivo Activity and Toxicity: Tuberculous mice were protected for at least 21 days beyond a 21-day treatment period; other antituberculosis drugs, such as streptomycin, paraaminosalicylic acid (PAS), and amithiozone (Tibione), failed to do so.[10] In the monkey tuberculosis has a rapid course, owing to the animal's low immunity. Zeiper and Lewis[11] treated a Macacus rhesus monkey with isoniazid after intranasal infection with a virulent strain and produced clinical arrest of the disease, with good drug tolerance. Isoniazid was very active against experimental tuberculosis in guinea pigs and rabbits infected with human strains, even though in some instances treatment was delayed for 21 days. Isoniazid was also found to produce a significant increase in survival time of tuberculous mice.[12]

Lepri and Catalfi[13] injected the anterior chamber of the right eye of 52 rabbits with 0.1 mg. of virulent tubercle bacilli. Ten rabbits were used as controls; 20 were treated with isoniazid, 10 mg. per kilogram a day; 11 were treated with streptomycin and isoniazid, 6 mg. per kilogram per day, and 11 received one of the following drugs in large dosage: streptomycin, neomycin, oxytetracycline (Terramycin), and paraaminosalicylic acid. The treatment was started 24 hours after the injection. In the group of 20 rabbits treated with 10 mg. per kilogram per day only 1 showed any signs of ocular infection. In this same group treatment was discontinued on the 25th day in 12 rabbits, and during the subsequent 20 days no change was noted in the eye. The remaining eight rabbits on treatment developed no ocular lesions. Fifteen days after injection of the control group, isoniazid was started. In four of these rabbits showing florid intraocular tuberculosis the lesions regressed rapidly. The group receiving the combined isoniazid-streptomycin therapy showed no inflammation after 20 days of treatment.

Toxic manifestations following large doses in laboratory animals have included central nervous system stimulation, excitement, convulsions, anorexia, weight loss, ataxia, tremors, prostration, jaundice, and death.[2] In dogs most of these side-effects were found to be reversible and there was good correlation between plasma peak levels and toxicity. The experimental maximum oral doses in mice, rats, and dogs agreed with those calculated on the basis of relative body surface area.[2]

In vivo experiments[4] on various species of animals revealed that isoniazid was less toxic than other isomers of nicotinic acid, and there was little variation with route of administration. There was some variation in absorption due to species differences. In acute toxicity studies[4] deaths were due to respiratory failure.

† References 7 and 8.

Chronic toxicity studies revealed significant changes in red cell count, white cell count, and hemoglobin levels only on high dosage. Prolonged lower dosage levels produced no change in the blood cellular constituents or the hemoglobin level. From the mass of data on animal studies has come the conclusion that doses of 2 to 5 mg. per kilogram are least likely to produce toxic manifestations or pathologic changes.

Activity and Toxicity in Man: Robitzek and Selikoff ‡ used isoniazid in patients with pulmonary tuberculosis not responding to any other method of treatment. They noted rapid reversal of the general toxic manifestations of far-advanced tuberculosis. There was increased weight, decrease in cough and sputum volume, decreased fever, some clearing of reversible roentgenologic changes, decreased Gaffky counts, and some negative sputums. These authors have also reported improvement of patients with tuberculous laryngitis, otitis media, glossitis and enteritis. The dosage was 3 to 4 mg. per kilogram a day. They noted no local irritation of any portion of the alimentary tract on oral administration, nor did they encounter any allergic manifestations. They did see vertigo, hyperreflexia, constipation, urinary bladder retention, nausea, vomiting, twitching of the extremities, insomnia, and drowsiness. Most of these manifestations disappeared on continued usage. No change in liver function, kidney function, or myocardial efficiency could be demonstrated. No change in the blood constituents or hematopoietic systems was noted other than a mild, reversible decrease in the hemoglobin level and mild eosinophilia.

Mount and Ferebee [17] reported a 20-week cooperative study of 290 patients selected at random to compare the efficacy of isoniazid, streptomycin-isoniazid, and streptomycin-paraaminosalicylic acid in pulmonary tuberculosis. All patients studied were susceptible to streptomycin. Roentgenographic improvement was best in the groups receiving isoniazid or streptomycin-isoniazid. A comparison on a laboratory and clinical basis, however, revealed less marked difference in the three regimens. The conclusion of these authors was that isoniazid is emerging as an extremely effective short-term therapeutic agent, but that it should be used with streptomycin or PAS or both.

Favorable reports § have also appeared in the foreign literature, revealing results which were similar in most respects to those of Robitzek and Selikoff and of Mount and Ferebee.

Brief contributions on the use of isoniazid or its isopropyl derivatives for tuberculous meningitis,‖ genitourinary tuberculosis,[23] and tuberculosis of the bone [24] have been made by various observers, with essentially favorable results in small series of cases.

Several less favorable reports and two advising caution have appeared. Tanner, Wanner, and Ramer [25] studied the efficacy of isoniazid in 114 patients and were unable to classify more than 17 as improved, although one-third became sputum-negative. They reported complications of exudative reactions, increased tempera-

‡ References 14 through 16.

§ References 18 through 20.

‖ References 21 and 22.

ture, increased expectoration, and increased auscultatory findings. Their opinion was that some of the increased appetite might be a nonspecific therapeutic effect. Studies in Britain ¶ failed to show that isoniazid was of any considerable benefit when used alone, although it did increase the efficacy of PAS and streptomycin. Their clinical, roentgenologic, and laboratory studies failed to confirm the high rate of improvement noted by others, and in one series [27] a high relapse rate after initial improvement was noted while the patients were still on isoniazid.

Wilkind and Willner [28] stated that isoniazid does have an antituberculous effect in humans but felt that this effect primarily combats the systemic toxicity and to a less extent the local lesions of the disease. Caution regarding the use of isoniazid in epileptic patients was advised by Fetterhoff, Holmes, and Martin,[29] who reported the death in status epilepticus of an epileptic patient: Concurrent use of barbiturates is strongly advised in such patients.

In a review of the use of isoniazid in 100 patients, Wacker and Bonard [30] noted an increased coagulation time in one-third but no change in bleeding time or prothrombin time. They mentioned clinical manifestations of increased bleeding tendencies in a number of patients. In diabetic patients with pulmonary tuberculosis isoniazid has caused an increase in insulin requirements, possibly due to increased appetite.#

Resistance to Isoniazid: Various reports of resistance to isoniazid * in vitro reveal the following important facts: (1) Resistance is often not overcome by increase in concentration of isoniazid; (2) sensitivity to streptomycin is not influenced by emergence of resistance to isoniazid; (3) tubercle bacilli exposed to streptomycin and isoniazid together do not develop resistance to either drug after as long as four weeks' incubation; (4) resistance to isoniazid can occur in one step, but no cross resistance with other antituberculosis agents is demonstrable; (5) isoniazid and streptomycin are synergistic; (6) in human strains of the Myco. tuberculosis there are a significant number of bacteria resistant to isoniazid which have not come in contact with the drug at any time.

In vivo resistance studies † have demonstrated some correlation with in vitro studies and have revealed the following facts: (1) the synergistic action of isoniazid and streptomycin; (2) in some instances, the rapid development of resistance to isoniazid; (3) markedly delayed resistance when streptomycin is used concurrently with isoniazid, and (4) effectiveness of isoniazid against organisms resistant to PAS and streptomycin.

In a recent report [40] bacillary resistance to isoniazid existed at the end of one month in 11% of patients with pulmonary tuberculosis, at the end of two months in 52%, and at the end of the third month in 71%. Lack of roentgenologic progress paralleled this increased resistance. These results all speak loudly against the indiscriminate use of isoniazid and indicate that it should be combined with dihydrostreptomycin, streptomycin, or PAS, or a combination of these drugs.

¶ References 26 and 27.

References 31 and 32.

* References 33 through 37.

† References 38 and 39.

II. CLINICAL STUDY OF ISONIAZID IN TUBERCULOUS UVEITIS

This study was limited to endogenous uveitis, and a small series of 22 cases treated with isoniazid is reported.‡ We began our study before it was recommended that isoniazid be used in conjunction with other antituberculosis drugs and in most cases have continued to use it alone for experimental purposes. We deliberately included 11 cases in our series which we believed were not tuberculous and treated them with isoniazid as a control on the therapeutic response to isoniazid observed in those cases that were considered tuberculous. Since it is impossible to make a positive diagnosis of tuberculosis, we classified the diagnoses of tuberculous etiology on the basis of their reliability as "unlikely" (11 cases), "possible" (5 cases), and "very likely" (6 cases). Thus, 11, or one-half, of our cases were considered not tuberculous, and 11, or one-half, were considered to be possibly or very likely of tuberculous origin. The diagnoses were made after a thorough laboratory and clinical survey, similar to that outlined by Woods.§ The clinical response to isoniazid was classified as good, fair, or poor. A comparison of the likelihood of tuberculous etiology and the degree of favorable response to isoniazid is presented in Table 1. From this Table a correlation between the likelihood of tuberculous uveitis and the

TABLE 1.—*Relationship Between Likelihood of Tuberculous Etiology and Response to Isoniazid*

Likelihood of Tuberculosis	Response to Isoniazid		
	Good	Fair	Poor
Very likely	3	2	1
Possible	1	2	2
Unlikely	0	2	9

clinical response to isoniazid may be observed. The more likely the diagnosis of tuberculous etiology, the more favorable was the response to isoniazid. Although these results probably have some validity, the following sources of error are patent: (1) the small number of cases; (2) the difficulty of making an etiologic diagnosis in endogenous uveitis; (3) the difficulty of evaluating therapeutic response in a heterogeneous group of cases, in which the natural course for some is spontaneous improvement and for others, continued deterioration, and (4) the difficulty of making an impartial judgment as to response. It was impossible to have an outside and impartial ophthalmologist make these decisions since it was necessary to follow the patients carefully in order to form an opinion.

Side-Reactions.—Isoniazid was accepted without any important general toxic effects. Two patients who experienced nausea and vomiting were able to continue when the dose was reduced. In regard to the eye, it has been our impression that isoniazid may have aggravated the hemorrhagic tendency of some of the fundus lesions in our patients. This possibility needs further investigation.

Patients frequently reported an increase in appetite, energy, and feeling of well-being. This subjective improvement was more dramatic than the objective response in many cases. In Table 2 it can be seen that there is no correlation between

‡ Observed and treated in the Uveitis Clinics of the Departments of Ophthalmology of the Indiana University Medical Center and the Indianapolis General Hospital.

§ References 41 to 43.

this subjective type of response and the likelihood of tuberculous etiology. Table 3 demonstrates no correlation of this subjective type of response with the objective response to isoniazid, but in Table 4 we do find a correlation with race. Our Negro patients were much more likely to report a favorable subjective response. Our series is too small to warrant conclusions, but this point should be investigated in a larger series of patients. It will be interesting to learn what action of isoniazid produces this subjective type of improvement, since in our study this improvement bears no correlation with the likelihood of tuberculosis; nor does it appear to be due to central nervous system stimulation, since many patients report that they sleep

TABLE 2.—*Relationship Between Subjective Improvement and Likelihood of Tuberculous Etiology*

	Subjective Response		
Likelihood of Tuberculosis	Pronounced	Moderate	Slight or Absent
Very likely	1	3	2
Possible	0	3	2
Unlikely	3	4	4

TABLE 3.—*Relationship Between Subjective Improvement and Objective Response to Isoniazid*

	Subjective Response		
Objective Response to Isoniazid	Pronounced	Moderate	Slight or Absent
Good	0	2	2
Fair	3	2	1
Poor	1	6	5

TABLE 4.—*Relationship Between Subjective Improvement and Race*

	Subjective Response		
Race	Pronounced	Moderate	Slight or Absent
Negro	4	1	1
White	0	9	7

better after taking isoniazid. It is possible that the nonspecific increase in weight and sleep may be of some systemic therapeutic value.

Isoniazid as a Diagnostic Aid.—Since our early experience with isoniazid indicated that the more likely the diagnosis of tuberculosis the better was the response to isoniazid, we began to use isoniazid in therapeutic trial as a diagnostic aid. Also, since our cases in the "very likely" (C) series tended to evince improvement in one or two weeks, our present impression is that a trial of isoniazid therapy for three weeks should be adequate and that a definite response should be noted within this time. We do not recommend, however, the use of isoniazid as a routine diagnostic aid, for the following reasons: (1) Resistance to isoniazid may develop when it is used alone; (2) some strains of tubercle bacilli are initially resistant to isoniazid, so that a negative response does not rule out tuberculosis; (3) rapid, spontaneous improvement is frequently noted without specific therapy, and the use of isoniazid

at such times would lead to a false-positive response. We feel that one should continue to rely on a thorough laboratory and clinical survey, such as that outlined by Woods.[43]

The "Rebound Phenomenon" as a Diagnostic Aid.—Woods first described the "rebound phenomenon" and demonstrated its development histologically in rabbits.[44] The "rebound phenomenon" does not refer to recurrence of inflammation when cortisone is stopped; rather, it refers to the development of a severe exacerbation in tuberculous eye disease. While the patient is on cortisone, the inflammation may be relatively quiet, but during this period tubercle bacilli are multiplying and the normal fibrotic protective mechanism is inhibited. Once cortisone is stopped the original inflammation becomes much worse. The typical case is that of tuberculous nodular iritis. During topical use of cortisone the inflammation decreases, but 24 to 48 hours after cortisone is discontinued a rapidly developing tuberculoma appears in the iris and bursts through its anterior surface. Woods has warned of this danger from cortisone therapy.[44] Our experience supports this view and we recommend that cortisone not be used in cases of uveitis believed to be tuberculous. If for some reason cortisone is used and the patient develops a severe exacerbation of inflammation upon its discontinuance, we feel that the diagnosis of tuberculosis is greatly strengthened. The patient should be started immediately on bed rest, isoniazid, streptomycin, dihydrostreptomycin, etc. Whether a patient can develop the "rebound phenomenon" while on antituberculosis drug therapy must await further study. Patients are frequently on cortisone when first referred. In cases not considered tuberculous, we have in some instances stopped the cortisone abruptly as a diagnostic aid in ruling out tuberculosis. We have less faith in the absence of the "rebound phenomenon" as a diagnostic aid than in its presence, since it is yet unknown whether all cases of tuberculous uveitis can develop a "rebound phenomenon" and it is yet to be determined what dosage of cortisone is necessary before it can occur.

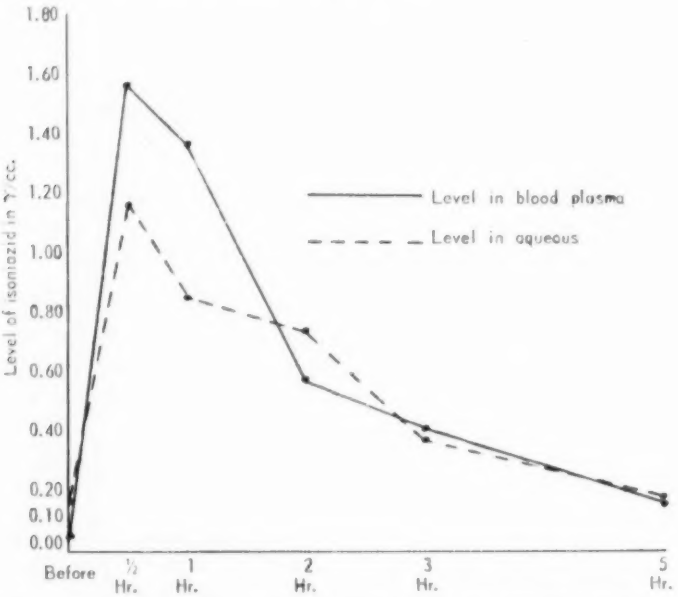
Dosage and Duration of Isoniazid Therapy.—We have not answered the question of optimum dosage of isoniazid therapy but shall continue to base our dosage level on the general literature about this drug. At the present time the recommended dosage is 3 to 5 mg. per kilogram per day. Although this dose is well tolerated, a smaller amount of isoniazid may be adequate when isoniazid is used with other agents.[8] Neither do we know how long isoniazid should be continued. In general, we have been hesitant about stopping isoniazid and have usually continued therapy for several months after any evidence of activity. Case C-2 appeared to have a mild relapse a few weeks after five months of isoniazid therapy, but the apparent flare-up may have been due to recently instituted tuberculin desensitization, since the flare-up spontaneously subsided. We have observed no other instance of apparent reactivation in the cases in the "very likely" series. Case B-2, in the "possible" series, may have had a severe relapse after only three weeks of isoniazid therapy. This case points up the possible danger in stopping isoniazid too early.

III. EXPERIMENTAL STUDY OF PASSAGE OF ISONIAZID ACROSS THE BLOOD-AQUEOUS BARRIER OF THE RABBIT

Since isoniazid had already been shown to be of value in tuberculosis, we felt that the main problem in ophthalmology was whether the drug would enter the eye in adequate amounts. Such a study was especially indicated since most antibiotics,

including streptomycin, pass the blood-aqueous barrier with difficulty. Studies on the ready penetration of isoniazid into the cerebrospinal fluid [8] would lead us to expect it to pass readily across the blood-aqueous barrier. Our study was limited to this feature.

Method.—After preliminary trials, 12 adult pigmented rabbits were used. Isoniazid was injected intravenously into the marginal ear vein in a dose of 1.5 mg. per kilogram. This dose was selected to simulate the clinical use of isoniazid, as it is frequently given as 1.5 mg. per kilogram b.i.d. or t.i.d., in the form of tablets by mouth. Absorption by mouth is rapid and gives plasma levels simulating the intravenous route. The intravenous route was used in the experiment for accuracy and for ease of administration. Six time intervals were studied: before intravenous injection (control), and one-half, one, two, three, and five hours. Four rabbits were used for each time interval and the means determined. Since two eyes were available, 24 aqueous samples were obtained without reusing an eye.



Level of isoniazid in the blood plasma of rabbits and in the aqueous humor of the same rabbits after intravenous injection of 1.5 mg. per kilogram of body weight. The values are in micrograms per cubic centimeter.

Values for blood plasma levels are shown by the solid line; values for aqueous level, by the broken line.

Five cubic centimeters of blood was obtained by ear drip for each plasma determination. Because of the small volumes of aqueous obtained, it was necessary to pool the four aqueous samples for each time interval. This was done both to increase the accuracy of the test and to average the results.

The isoniazid levels were determined by Dr. O. M. Helmer and Mr. Robert Sanders, of the Lilly Laboratory for Clinical Research, Indianapolis General Hospital. The following modification of the technique of Kelly and Post [45] was used: The *p*-dimethylaminobenzaldehyde reagent was prepared by dissolving 300 mg. in 5 cc. of absolute ethyl alcohol and adding 2 cc. of 12 N HCl. This change reduced the blank and increased the color of the unknown. Since an Evelyn photoelectric colorimeter was used, the total volume read was increased to 6 cc. and the color read at 440 μ.

The standard curve was prepared as follows: To 2.0 cc. of normal plasma various concentrations of hydrazide (1-10 γ) in 1 cc. of H_2O were added. Then 3.2 gm. of solid ammonium sulfate and 1.0 cc. of 0.5 N NaOH were added and the mixture shaken for 30 minutes with 40 cc. of a mixture (1:4) of amyl alcohol and ether U. S. P. Twenty-five cubic centimeters of the clear organic phase was poured into another bottle, containing 4 cc. of 0.1 N HCl. The bottle was shaken for 10 minutes and allowed to stand for a few minutes for the separation of the layers. Three cubic centimeters of the lower acid layer was drawn off with a pipette and transferred to a calibrated 15 cc. centrifuge tube. Then 1 cc. of the phenylhydrazine reagent and 0.5 cc. of 6 N HCl were added. The tube was heated to 100 C. in a boiling water bath for 45 minutes, cooled to room temperature, and made up to 6 cc. with 0.1 N HCl. The color was read as described above.

The determination in the unknown plasma was done as follows: Two cubic centimeters of plasma and 1 cc. of H_2O were treated as described for the standard curve. The unknown pooled aqueous humor samples were treated in the same manner except that the total volume of aqueous obtained was only from 0.5 to 1.0 cc. of fluid. This fluid was increased to 2 cc. with distilled water before proceeding, but corrections for this dilution were made.

Results.—The Chart demonstrates that isoniazid and/or its metabolic products pass readily and rapidly from plasma to aqueous humor. The peak level in the aqueous (one-half hour) was three-fourths that of plasma. Isoniazid not only enters the anterior chamber rapidly but also leaves it rapidly at about the same rate that it leaves the plasma. Isoniazid had almost completely disappeared from both plasma and aqueous humor by five hours.

COMMENT

We were able to compare the aqueous values in rabbits with those in one patient (Case A-7). In this case, repeated paracentesis of the anterior chamber enabled us to learn that the level of isoniazid was apparently as high as or higher than that observed in rabbits. The accuracy of the level obtained from one aqueous sample of a patient is low, however, because of the small volume obtainable for testing.

Simonelli and Rizzini [46] found a concentration of 40 γ per cubic centimeter in the aqueous humor of rabbits following an injection of 50 mg. intravenously and a concentration of 140 γ per cubic centimeter after 50 mg. injected subconjunctivally. These large injections produced aqueous humor concentrations much in excess of peak level of 1.18 γ per cubic centimeter and demonstrate again the ease with which isoniazid enters the eye. Caution regarding the validity of isoniazid levels must be observed, however, because of the gross character of the various techniques in use.

Our one patient with sarcoid (Case A-1) evinced a definite, but delayed, improvement with isoniazid. The ocular status improved six weeks after isoniazid was first used and four weeks after a second course of therapy. These favorable responses were probably coincident spontaneous improvements, but the possibility that isoniazid may prove to be of value in sarcoid should receive further investigation.

Only one case believed tuberculous (C-6) failed to respond to isoniazid. Three possible explanations occur to us: (1) The case was not tuberculous; (2) the dose of isoniazid was inadequate, or (3) the tubercle bacilli were resistant to isoniazid. The third possibility seems to be most likely. It has been demonstrated that some strains of tubercle bacilli are initially resistant to isoniazid and others rapidly develop resistance when isoniazid is used alone.

SUMMARY

I. *Attributes of Isoniazid* (review of the literature).

Favorable	Unfavorable
1. Isoniazid is as active against intracellular as against extracellular tubercle bacilli (superior to streptomycin).	1. A significant number of tubercle bacilli are initially resistant to isoniazid.
2. Isoniazid is apparently less toxic than streptomycin or dihydrostreptomycin.	2. Resistance of tubercle bacilli to isoniazid may develop rapidly.
3. Isoniazid is easy and economical to take in tablet form.	3. Other antituberculosis agents should be used with isoniazid.
4. Sensitivity to other antituberculosis agents is not influenced by emergence of resistance to isoniazid.	4. Isoniazid should be used with barbiturates in patients with epilepsy.
5. Tubercle bacilli exposed to streptomycin and isoniazid togther do not develop resistance readily to either drug.	5. Isoniazid may produce an increased coagulation time.
6. Isoniazid and streptomycin appear to be synergistic.	6. The drug may accumulate excessively if renal function is impaired.
7. Isoniazid may be effective against tubercle bacilli resistant to PAS and streptomycin.	7. Isoniazid increases insulin requirement of diabetics.

II. *Clinical Effect of Isoniazid in Tuberculous Uveitis.*

1. In general, the more likely the diagnosis of tuberculous etiology, the better was the objective response to isoniazid.

2. The objective response to isoniazid in those cases considered tuberculous occurred after one to two weeks of therapy.

3. A subjective improvement is frequently observed which bears no relationship to objective improvement or likelihood of tuberculous etiology but does appear to be more pronounced in the Negro.

4. The use of isoniazid as a diagnostic aid is not recommended as a routine procedure.

III. *Experimental Study on the Passage of Isoniazid Across the Blood-Aqueous Barrier.*

Isoniazid passes readily and rapidly across the blood-aqueous barrier of rabbits.

CONCLUSIONS

Isoniazid appears to be of value in the treatment of tuberculous uveitis. It is relatively nontoxic, passes readily across the blood-aqueous barrier, and is easy to take in tablet form. Clarification of its value will necessitate its use in a much larger series of patients, observation over a longer period, and studies of the relative value of various separate and combined antituberculosis agents. We recommend its use

at this time, but with the following provisions: (1) that a thorough diagnostic survey be made, and (2) that it be used in conjunction with other antituberculosis measures, such as streptomycin and dihydrostreptomycin, PAS, tuberculin desensitization, and rest.

ADDENDUM

Report of Cases

In these cases isoniazid was given in a dosage of 3 to 4 mg. per kilogram a day unless otherwise stated. Details of the clinical picture and diagnostic work-up are not included.

A. Cases Classified as of "Unlikely" Tuberculous Origin.—Case A-1.—B. M., a Negro housewife aged 48, had Boeck's sarcoid with nodular iritis. Treatment had consisted of paracentesis, administration of atropine and salicylates, and local use of cortisone (after which no rebound phenomenon developed). She complained of pain, redness, sensation of scratchiness, and decreased visual acuity in the left eye. She was placed on isoniazid (6 mg. per kilogram a day) on July 18, 1952. There was no apparent change in the iris nodules and no other improvement until six weeks later, when both the visual acuity and the inflammation definitely improved, although the nodules remained unchanged. Isoniazid was discontinued on Dec. 10, 1952. After several weeks there was a relapse in the inflammation, and treatment with isoniazid was restarted on Jan. 14, 1953. One month later the visual acuity had improved from 20/100 + 2 to 20/30 — 2. The response to isoniazid is difficult to judge in this case of sarcoid because of the delayed response and because the patient had evinced similar fluctuations in her clinical course previously. There was definite decrease in pain, injection, and conjunctival burning, which had been persistent prior to treatment. She felt better systemically than at any time since the onset of her disease and so has been most desirous of continuing isoniazid. She has had no adverse side-effects. The response to isoniazid was classified as "fair."

Case A-2.—J. R., a white boy, aged 6 years, was seen in July, 1952, with a red right eye and keyhole pupil. Visual acuity was 20/100. He had a moderate flare and a moderate number of cells, a few keratic precipitates, and a cyclitic membrane superiorly in the right eye. Treatment was instituted with cortisone and atropine locally, and there was no rebound phenomenon following discontinuance of cortisone. He was placed on isoniazid and remained on this treatment for five weeks, at the end of which the eye showed slight improvement, such as would have been expected with atropine alone. No side-reactions were noted. With discontinuance of isoniazid no change was detected. The results of isoniazid therapy were classified as "poor."

Case A-3.—M. S., a Negro housewife aged 39, was first seen in March, 1952, with a history of recurrent attacks of iritis of each eye, beginning in 1947. The complaints were decreased vision and a feeling that the eyes were "weak." A cataract extraction had been done on the left eye. The visual acuity was 20/200 (R. E.) and 1/200 (L. E.). There were severe bilateral flare but no cells; tension was 8 mm. Hg in the right eye and too low to read in the left eye. She was given isoniazid and local atropine for five weeks. There were no side-reactions except for slight nausea on occasion, but because of this the dose was reduced from 3 to 1.5 mg. per kilogram a day. Treatment resulted in no objective improvement, although the patient had an increased feeling of well-being and stated that her eyes felt "stronger." The results were classified as "poor."

Case A-4.—S. C., a 49-year-old white woman factory worker, first developed iritis in the left eye in February, 1951, followed later by iritis in the right eye. This process has continued, with some exacerbations and remissions but with a chronic course. Treatment consisted of atropine and local cortisone, and there was no rebound phenomenon on discontinuance of cortisone. She was placed on isoniazid on Dec. 8, 1952, and kept on it for 18 days, without any apparent change. The response to isoniazid was classified as "poor." The eye became white, and vision improved after a tonsillectomy.

Case A.5.—T. S., a white woman aged 45, was seen in September, 1952, complaining of blurred vision in both eyes. The onset was in May, 1952. Both eyes revealed very fine keratic precipitates, a mild flare, and a fair number of cells. The visual acuity was 20/30 + 2 (R. E.)

and 20/30 — 2 (L. E.). She had been using local atropine and cortisone, and this therapy was continued. She was started on four weeks of isoniazid therapy on Nov. 10, 1952. The iridocyclitis continued to improve, as it did before and after isoniazid therapy. On discontinuance of cortisone therapy there was no rebound phenomenon. The response to isoniazid in this case was classified as "poor."

Case A-6.—E. M., a Negro aged 34, complained of pain and a film over the left eye. Symptoms had begun insidiously two weeks previously. Examination of the left eye revealed medium-sized keratic precipitates and a severe flare with a fair number of cells. Posterior synechia had been broken by previous medication. The fundus was not well visualized, but no lesions were detected. He was continued on the local atropine and cortisone which he was using when first seen, but the eye continued to get worse; much fluffy white material appeared on the anterior lens capsule. He was started on penicillin for acute tonsillitis. When he recovered from this infection, isoniazid was started, on Jan. 21, 1953. When he was next seen, five days later, the ocular process had continued its downward course; vision was limited to finger counting at four in. (10 cm.), and the fundus was not visible, apparently because of severe vitreous exudate. Isoniazid was continued until Feb. 16, 1953, without any apparent effect on the course of the disease. During this period he was given typhoid vaccine intravenously, with some improvement. On the same date cortisone was stopped in order to test for the rebound phenomenon. No rebound phenomenon developed, and the ocular condition continued its downward course. The response to isoniazid was classified as "poor."

Case A-7.—J. T., a 38-year-old white man, developed a red left eye in September, 1952. Vision was 20/15 (R.E.) and 20/50 (L.E.). The right eye was mildly involved, with mutton-fat keratic precipitates, flare and cells, and edema of the disc. There was a severe chorioretinitis in the superonasal quadrant of the left eye. The visual acuity rapidly decreased. The arterioles had a silver-wire appearance, with minute periarteriolar hemorrhages and sheathing in the superotemporal quadrant. The entire retina was edematous. There was a large, almost confluent, exudative area of chorioretinitis without hemorrhages in the periphery. During this hospitalization the patient was treated for two weeks with isoniazid, thiazolsulfone (Promizole), atropine, dihydrostreptomycin, and intravenous typhoid therapy.

After two weeks on isoniazid, the visual acuity fell to finger counting at 10 ft. (3 meters). This patient was followed as an outpatient very briefly and was readmitted for further treatment. He received intravenous typhoid therapy with salicylates between bouts of fever and chlortetracycline (Aureomycin) and dihydrostreptomycin. During this admission the patient was given no isoniazid, and his eye improved slightly. The third admission was on Nov. 21, 1952, because of a relapse, with further loss of vision. Paracentesis was carried out repeatedly during this third admission, and treatment was restarted on isoniazid, atropine, acetylsalicylic acid, and vitamin B complex. The isoniazid level of two of the aqueous samples was found to be as high as or higher than the levels found in the rabbits tested in Part III of the report. Following four more treatments with intravenous typhoid vaccine, the patient was again discharged, at which time the visual acuity was down to counting fingers at 2 ft. (60 cm.). The toxoplasmin skin test was 1+. The complement fixation test for toxoplasmosis was 4+ in 1 : 16 dilution and did not vary. The Sabin dye test, done by Dr. Harry Feldman, was positive in a 1 : 1,024 titer, a result which he considered significant. It is felt that this uveitis was due to toxoplasmosis. The response to isoniazid was classified as "poor."

Case A-8.—R. S., a 33-year-old white foreman, gave a history of four recurrent attacks of iritis in the left eye in four years. The history revealed rheumatoid arthritis, for which he was hospitalized in 1947 and 1948. He was seen two weeks after the onset of gelatinous iritis, with a visual acuity of 20/20 in the involved eye. He was using atropine and cortisone locally, and these were continued. On Jan. 21, one month after he was first seen, the eye was somewhat improved and he felt better generally, but on the next visit, on Feb. 2, the vision had fallen to 20/50. He was started on isoniazid at this time. There was a questionable smudgy edema of the macula. At the next visit, on Feb. 9, the vision had fallen to 20/200. The macular area was now definitely gray, slightly elevated, and smudged in appearance. With red free light there appeared to be a hole in the macula. The anterior segment was perhaps slightly improved. After three weeks of treatment with isoniazid it was stopped because of no apparent benefit. The response

was classified as "poor." This patient had an antistreptolysin titer of 100, which fell to 12 after decrease in the anterior segment activity. The impression in this case was that of chronic nongranulomatous iridocyclitis with secondary vascular toxic involvement of the macula.

CASE A-9.—P. B., a 17-year-old white male student, noticed decreased vision and black streaks in front of his left eye on Feb. 25, 1953. He had always had poor vision, apparently from congenital central chorioretinitis, atrophic on admission. He gave a history of bad teeth and tonsils, many head colds, and drinking raw milk as a child. Examination of the left eye revealed fine greasy keratic precipitates and fresh, elevated, hazy gray choroiditis with associated field defect immediately above the disc. There were large vitreous floaters and many cells in the retrolental space. Isoniazid was started on March 4, 1953. The drug was continued for three weeks, with no apparent change in the choroiditic lesion. The response to isoniazid was classified "poor."

CASE A-10.—P. J., a 27-year-old photographer, noticed smoky vision in the right eye on Feb. 11, 1953, after use of a microscope. Slit-lamp examination revealed flare and cells and small keratic precipitates. In the fundus there was an area of creamy-colored, fluffy chorioretinitis, roughly triangular in shape, in the superonasal equatorial region. The lesion appeared elevated and active. While he was undergoing a diagnostic work-up, the lesion was observed to regress slowly; he was started on isoniazid therapy on March 2, 1953, and was kept on this for three weeks, during which time improvement of the lesion continued steadily, such as would have been expected without therapy. The response to isoniazid was classified as "poor."

CASE A-11.—L. F., a 33-year-old Negro woman, was seen two weeks after the onset of poor vision in the left eye. The day before she had slipped and hit the left side of her head on a refrigerator. Visual acuity was 20/30 — 1 and 20/50. The anterior segment was normal. The fundus of the left eye revealed a slightly active, grayish, triangular, slightly elevated lesion in the superonasal quadrant with an adjacent superficial pigmentary disturbance. After an observation period of three weeks, during which time the lesion appeared unchanged, she was started on isoniazid. She reported that isoniazid made her sleepy and hungry but not tired and that she slept better at night. After three weeks the isoniazid was stopped and the fundus lesion appeared improved, with little evidence of activity. The response to isoniazid was classified as "fair."

B. Cases Classified as of Possible Tuberculous Etiology.—CASE B-1.—V. B., a white woman secretary aged 40, gave a history of bilateral iritis 13 years previously, followed by three subsequent attacks. The last attack occurred after streptomycin became available, and it was used with good results, but with the most recent attack this treatment did not give any improvement. She had smoldering iritis and keratitis and complained of photophobia, injection, and pain in the right eye. She was started on isoniazid. Concurrently, but intermittently, she received local cortisone, streptomycin, PAS, and OT desensitization. Inadvertently, she took 600 mg. of isoniazid per day, which was twice her usual dose. The side-reactions were dizziness, nausea, and vomiting. After seven days on the double dose, she took none for three days, while the side-reactions subsided. At the time of this report she is improved and feels that isoniazid has been of help, although it is impossible to say which of the various treatments has caused improvement. The response to therapy was classified as "fair."

CASE B-2.—F. M., a white housewife aged 44, had chronic granulomatous uveitis involving the anterior and posterior segments of the left eye. She had previously received treatment with penicillin, atropine, and local cortisone, with little effect. She did improve some after discontinuance of cortisone (the opposite of a rebound phenomenon). At the time this patient was started on isoniazid, July 18, 1952, the only concurrent treatment was atropine. She complained of blurred vision in the left eye (20/100). In the peripheral fundus were slightly elevated cream-colored plaques. This patient had a history of a positive Wassermann reaction, but the uveitis did not respond to two courses of penicillin. She also gave a history of having received treatment for diabetes. After one month on isoniazid, the visual acuity improved from 20/100 to 20/40 and the anterior segment activity was definitely better. After three weeks of therapy isoniazid was stopped. Within two weeks a severe macular hemorrhage developed, although the peripheral choroidal lesions remained unchanged. The visual acuity decreased to perception of hand movements at 2 ft. Isoniazid was restarted at this time, but without any apparent effect. The results of isoniazid therapy were classified as "fair" because of improvement during the initial course of isoniazid.

CASE B-3.—M. V., a Negro woman factory worker aged 30, had chronic bilateral uveitis and keratitis. She had received atropine, salicylates, and antisyphilitic penicillin therapy. She complained of a painful sore right eye with blurring of vision for distance and near (20/50). Isoniazid and local atropine were started April 11, 1952, but after two months contact with the patient was lost. During this period the cooperation of the patient was poor, and there was no definite improvement from the use of isoniazid. There was decreased eye discomfort and an increased feeling of well-being, but there was no change in the slit-lamp picture or the vision. The results were classified as "poor."

CASE B-4.—R. H., a white woman aged 34, was seen in October, 1952, complaining of a red right eye and blurred vision (20/50 + 2). The right eye revealed fine keratic precipitates, questionable Koeppe nodules, a mild flare, and few cells. There was a mildly active peripheral choroiditis from 8 to 11 o'clock, with a slightly hazy vitreous. The patient had been using local atropine and cortisone. This was continued and the patient placed on isoniazid on Nov. 10, 1952, as a therapeutic trial. After three weeks this therapy was discontinued to determine the effect of withdrawal. The anterior segment activity gradually decreased during and after isoniazid therapy. The mildly active choroiditis remained unchanged. It was felt that the response to isoniazid was "poor" and that the gradual improvement in the iritis was due to the natural course of the disease.

CASE B-5.—F. B., a white woman factory worker aged 18, was seen at the onset of a solitary "tubercle" of the choroid (visual acuity, 20/25). She was started immediately on isoniazid. There was a gray-white, soft, spherical protuberance just superotemporal to the macula with some surrounding hemorrhage. Concurrent therapy consisted of rest, phenobarbital, and decreased use of tobacco and caffeine. Within five days after isoniazid therapy had been started the "tubercle" gave evidence of regression, and the regression continued steadily. The surrounding hemorrhage, however, increased in size and severity to include even the preretinal type. Edema in the contiguous macula simulated that of central serous retinopathy. With this severe reaction at the macula, the visual acuity fell to a low of 17/200. Two months after the onset, the blood had all been absorbed but had left a dense white plaque 3 to 4 disc diameters in size in the macular area, which appeared to lie within the substance of the retina. This plaque, which had the appearance of a permanent residue, was absorbed over the following month and disappeared completely. The only residue after six months of treatment was a flat, mildly pigmented, atrophic spot at the site of the previous "tubercle," and mild stippling at the fovea. The response was classified as "good." Treatment was stopped on Feb. 9, 1953, and a follow-up on April 4, 1953, revealed normal vision and no evidence of activity in the hyalinized scar.

C. Cases Classified as "Very Likely" Tuberculous.—CASE C-1.—J. B., a white physician aged 30, had a history of two attacks of choroiditis in the right eye at the ages of 6 and 25, which destroyed the central vision. On Feb. 14, 1952, an acute choroiditis and granulomatous iridocyclitis developed in the right eye. He was treated with dihydrostreptomycin and thiazolsulfone, atropine, tuberculin desensitization, salicylates, and hospitalization during which time he received intravenous typhoid therapy. Because of the violent anterior segment involvement he was treated temporarily with cortisone ointment and heat, without the rebound phenomenon on discontinuing cortisone. Concurrent dihydrostreptomycin and thiazolsulfone therapy, however, may have prevented a rebound phenomenon. After 72 days, dihydrostreptomycin was stopped, and isoniazid (3 mg. per kilogram a day) was started on April 30. By this time the severity of the process had greatly abated, but he still complained of blurred vision and photopsia. Concurrent therapy consisted of continued tuberculin desensitization and atropinization. After isoniazid therapy was started, there was no longer any flare or cells in the anterior chamber. The photopsia, bulbar injection, and vitreous have gradually improved until June 30, 1952, when he was last seen. A personal communication three months later stated that the improvement had been maintained. The response to isoniazid therapy was classified as "fair" because the drug was started too late in the course of the disease to give a good idea of its efficacy.

CASE C-2.—C. W., a white man aged 40, a sign painter, had a solitary "tubercle" of the choroid. There was a history of a sudden onset of hazy vision in March, 1952. There was a gray-white, elevated, soft spherical lesion about ¾ disc diameter superior to the macula of the left eye. Surrounding the "tubercle" was an extravasation of sanguineous and serous material into the retina of the macular region. The visual acuity was 20/200 + 1. Four days later the

"tubercle" and hemorrhage had increased, and the visual acuity had fallen to 10/200. On April 18, 1952, he was started on isoniazid, 3 mg. per kilogram a day. In eight days the "tubercle" had decreased in size, and the blood had partially been absorbed and had settled inferiorly. The picture continued to improve: The "tubercle" steadily became more atrophic, and the hemorrhage was gradually absorbed but left severe edema residues. After four weeks the visual acuity had improved to 20/40, but with the continuance of the healing process it fell to 20/50. At this time, which was five months after therapy had been started, isoniazid was stopped. He complained of frequency and polyuria while on isoniazid, but his appetite and weight had increased and he had a sense of well-being. When the drug was withdrawn he was more nervous and less satisfied. He changed ophthalmologists and received tuberculin desensitization. On Sept. 15 the "tubercle" appeared to have become reactivated and the vision was 20/100. Although this patient was on isoniazid for weeks after any evidence of activity, treatment may have been discontinued too soon or should have been restarted, or the flare-up of the "tubercle" may have been due to tuberculin desensitization, although the dose used was well below his skin sensitivity. He was seen again on March 16, 1953. The lesion was inactive and the vision 20/200. Because of the poor residual vision, the response to isoniazid was classified as "fair" despite the rapid resolution of the "tubercle."

CASE C-3.—F. W., a Negro molder aged 29 years, had bilateral granulomatous uveitis and typical tuberculous keratitis. This patient had received much previous treatment with cortisone, atropine, and typhoid H antigen. He had experienced the rebound phenomenon after discontinuance of cortisone. For two flare-ups he also received systemic dihydrostreptomycin and thiazolsulfone with definite improvement. For a subsequent flare-up, he was started on isoniazid on July 18, 1952. His visual acuity at this time was 20/30 (R. E.), and 20/10 (L. E.). He complained of blurred vision in both eyes, more pronounced in the left eye; of bilateral injection; of poor sleeping ability, and of constant tiredness and headache. Concurrent therapy consisted of atropinization and continued tuberculin desensitization. Objective and subjective improvement was noted after one week and after one month the visual acuity in the left eye had improved from 20/100 to 20/30. There was a decrease in flare and cells in both eyes; the keratic precipitates appeared harder and the corneas much clearer. There was an increase in weight of 10 lb. (4.5 kg.) after three months on isoniazid. All the subjective symptoms of poor sleeping habits, tiredness, and headaches had disappeared. The injection, of which he complained because of its cosmetic appearance, had improved markedly. After 16 weeks isoniazid was discontinued. There has been no relapse during an observation period of six months, during which time the vision has been about 20/20 in each eye. This case was our most valuable one, since we have followed the patient for several years and have observed the effect of various therapeutics, such as salicylates, local cortisone, dihydrostreptomycin and PAS, dihydrostreptomycin and thiazolsulfone, intravenous typhoid organisms, and, finally, isoniazid. All these therapeutic agents resulted in improvement, but cortisone was a bad choice because of the severe rebound phenomenon following its discontinuance. Isoniazid has resulted in the greatest and most permanent clearing of this man's chronic keratitis and uveitis. The response to isoniazid was classified as "good."

CASE C-4.—D. L., a white male student aged 17, developed severe chorioretinitis and was placed on systemic cortisone on June 1, 1952, for a period of three weeks, during which time there was marked improvement. The cortisone was then discontinued, and an exacerbation of the chorioretinitis developed, with the addition of severe iridocyclitis and keratitis. When the patient was seen, on Aug. 8, 1952, the cornea was diffusely edematous, making it difficult to detect the iris. The vision was perception of hand movements at 2 ft., and the eye was very red and painful. The local use of cortisone was gradually decreased, and he was started immediately on isoniazid. A dramatic improvement followed. After two months the eye was white and the cornea almost completely clear grossly. Despite severe vitreous strands the vision had improved to 20/100 on Dec. 23, 1952. The improvement on isoniazid was considered "good" because of the rapid subsidence of the keratitis and uveitis, despite the residual damage.

CASE C-5.—M. S., a white housewife aged 30, developed a painless loss of vision in the left eye some time in the year prior to being observed, which was discovered only during a routine check for employment. Her visual acuity on the first visit was 20/20 (R. E.) and 3/200 (L. E.). The eyes were normal except for the fundi. In the right eye there were small areas

of atrophic choroiditis. At the left macula was a grayish, disc-like elevation, measuring 1½ D. in height and 1½ disc diameters in width, surrounded by hemorrhage. The lesion resembled a disciform degeneration of the macula. The yellowish, hazy, elevated character of the lesion and the presence of a normal macula and peripheral atrophic choroiditis in the other eye made us suspect choroiditis. Before institution of isoniazid therapy, this lesion was carefully observed for two weeks, during which time no change occurred. After one week of isoniazid no change was noted, but after two weeks a striking change had occurred. The mass had shrunk to ⅔ disc diameter in size and appeared harder and darker, and the hemorrhage was much less. She felt better, had an increased appetite, and gained weight. At three weeks the vision had increased to 20/200 and the lesion was becoming pigmented. This pigmentation has increased. All the hemorrhage has disappeared and the vision has remained 20/200. The response to isoniazid was classified as "good" because of the dramatic response, despite the poor residual vision, vision having probably been irretrievably lost before isoniazid was started.

Case C-6.—T. N., a 49-year-old woman department store clerk, developed typical granulomatous iritis in each eye in mid-December, 1952, but did not go to an ophthalmologist until after Christmas. This was a severe reaction, with typical mutton-fat keratic precipitates. The patient's mother had had tuberculosis, which was cured while the patient was in high school. The patient was sensitive to 1:100,000 old tuberculin and had a calcified scar in her lung. The rest of the work-up was uninforming. She was placed on isoniazid (3 mg. per kilogram a day) on Feb. 5, 1953, and after three weeks there was no apparent response to medication. At this time, daily dihydrostreptomycin (0.5 gm.) and streptomycin (0.5 gm.) were added to the daily isoniazid dose and continued for two weeks, when the frequency of injections was reduced to two weekly. She was also started on tuberculin desensitization and bed rest at this time. After several weeks a slow but gradual improvement was noted. The response to isoniazid was classified as "poor."

The following ophthalmologists allowed us to include some of their patients in this study: Dr. Jack I. Taube; Dr. Harry Aldrich; Dr. Harlan H. Tyner; Dr. Robert T. Allen; Dr. Donald P. Bixler.

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POSTERIOR (ECCENTRIC) LENTICONUS

Report of First Case with Clinical and Histological Findings

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IT WAS in 1883 that Becker [1] gave the first anatomical description of posterior lenticonus in the rabbit, while the first clinical observation in man, by Meyer,[2] dates from 1888.

As far as the pathogenesis of posterior lenticonus is concerned, it was von Hess * who, on the basis of similar findings in the rabbit and the pig, put forward the theory that the condition was primarily the result of rupture of the posterior capsule of the lens, probably occurring at the embryonic stage, while he admitted that traction of the hyaloid artery might also play an important role.

Even though many authors have accepted this hypothesis, others have wondered whether the rupture of the capsule were not, in certain cases at least, an artifact produced by fixation.† This point of view is supported by the fact that 30 cases of posterior lenticonus in animals were described between 1883 and 1907, but only anatomically, and that since then only 3 cases have been observed, those by Merkel,[9] in 1927, in rabbits of the same litter, but with no rupture of the capsule!

With regard to traction of the hyaloid artery, it was Vogt ‡ especially who insisted that in man the remnants of the hyaloid artery are always found inserted on the nasoinferior side of the posterior lenticonus and that traction on this artery would not therefore seem to be the cause.

Since Meyer's first observation,[2] accounts of approximately 90 cases of posterior lenticonus in man have been published, but it is clear that an accurate clinical diagnosis became possible only after the invention of the slit lamp. Of the seven anatomopathological cases of posterior lenticonus observed in man, the eye was enucleated for glaucoma in three (Pergens,§ two cases; Gourfein-Welt,[14] one case), but only the histological examination showed lenticonus. The four other cases are concerned purely with anatomopathological findings, the lenticonus being accompanied by other malformations.‖ From a patient Doherty [19] extracted both lenses, affected

From the Ophthalmological Clinic of the University of Geneva.

Professor Franceschetti was foreign guest of honor at this meeting of the Section.

Read before the Section on Ophthalmology at the 102nd Annual Meeting of the American Medical Association, New York, June 3, 1953.

* References 3 through 5.

† References 6 through 8.

‡ References 10 and 11.

§ References 12 and 13.

‖ References 15, 16, 17, and 18.

with cataract, which five years before had shown posterior lenticonus, but histological examination gave no definite results.

As Bellows [20] emphasized, there is still no record of a case of posterior lenticonus with complete clinical and anatomopathological examination.

In March, 1950, we had the opportunity of examining a case of peripheral posterior lenticonus which had given rise to discussions as to the diagnosis.¶

REPORT OF CASE

D. G. (Clin. Observ. 9282), a boy, was born in 1946. The child was examined at the age of 3½ years, with the complaint of photophobia. After pupillary dilatation, the oculist noticed a cystic, brownish formation, localized behind the lens on the temporal side of the right eye. Later, a second pigmented mass was found on the periphery at 7 o'clock. Six months after the first examination, the two cystic formations seemed to have increased in volume. In view of the possibility of a malignant neoformation, the eventual necessity of an enucleation was discussed.

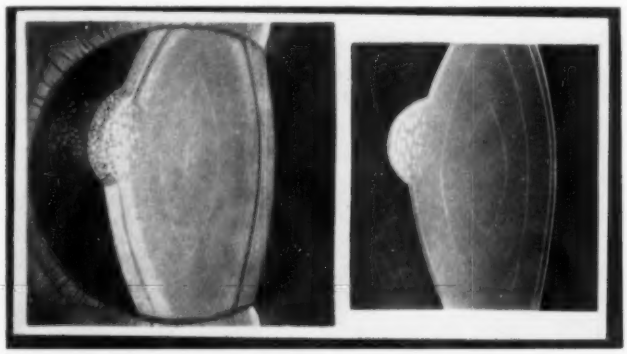

Fig. 1.—Eccentric posterior lenticonus (optic section): left, with a large beam; right, with a small beam.

When we made our examination in March, 1950, we were able to obtain the following findings: The physical and mental development of the child, then 4 years old, was quite normal. There was no consanguinity of the parents. On examining the right eye with the plane mirror, we could see through the dilated pupil a dark round disc at 10 o'clock which could be displaced in the direction opposite the movements of the mirror, and a second opacity, smaller and longer, on the periphery at 7 o'clock.

On examining the lens with the slit lamp, we noted near the large opacity, at 10 o'clock, a globular formation of the lens, with a marked backward convexity. This almost spherical crystalline ectasia was covered on the posterior surface by a dense, finely crackled layer of pigment, without any vascularization (Fig. 1). A few fine crystalline opacities were observed in the cortical layers, corresponding to the lenticonus. A second lenticonus was found on the periphery at 7 o'clock, but this was a much smaller and less regular one, shaped like a pear upside down. It was also covered with pigment on its posterior surface. The two lenticoni were linked by fine folds of the posterior crystalline capsule. Apart from the lenticonus, the curvature of the lens seemed almost normal. On the nasal side of the posterior surface of the lens the physiological remnants of the attachment of the hyaloid artery were visible, but there was no trace of a persistent hyaloid artery. The structure of the interior of the lens was preserved. The zones of discontinuity and the two embryonic sutures were faintly visible. There was no displacement of the embryonic nucleus.

¶ The clinical examination of this patient has already been reported.[21]

Comment.—It is well known that lenticonus is almost always found on the posterior pole, or very near it. In the cases of Attias [22] and of Mussabeili [18] there were two posterior ectasias, and in the case of Samoilov [23] the posterior lenticonus was somewhat eccentric.

The only known case of peripheral lenticonus discovered by one of us (A. F.) was published in Vogt's "Atlas." [24] The lenticonus was slightly curved and was situated in the temporoinferior quadrant, and it also was covered with pigment in its most peripheral part.

That we are dealing in our case with peripheral posterior lenticoni is confirmed by the presence of some typical optical phenomena. Indeed, the slit lamp clearly revealed to us the characteristic ring reflex around the ectasia, and especially the scissors reflexes described by Vogt [11] in 1926 and, independently of him, several months later, by Marsh.[25] When one brings the biomicroscopic slit near to the rim

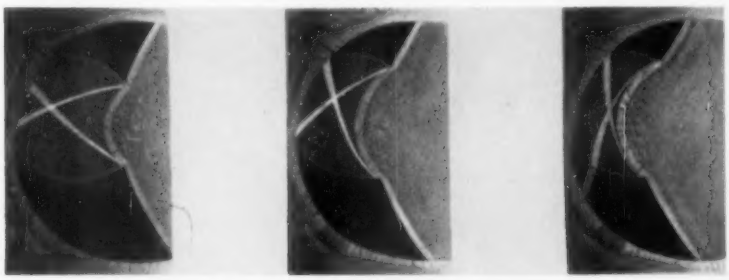

Fig. 2.—Eccentric posterior lenticonus: scissors movement of the reflexes.

of an axial lenticonus, one can see two cross reflexes on the surface of the posterior region of the lens. These reflexes approach each other vertically by a scissors movement and finally join when the beam of light is passed through the lenticonus. Vogt # attributed this phenomenon to the reflection of light on the opposite wall of the lenticonus, while Marsh * gave no explanation. With the help of a model, we have been able to show that these cross reflexes arise from the points at which the luminous slit touches the lateral edges of the lenticonus and at which the angle of incidence is so small that it produces a total reflection. In fact, when the optical cut is displaced through the lenticonus, the total reflection takes place at the point of intersection with the walls of the lenticonus. It is then that two scissors reflexes appear, approaching each other, to become a single line when the light beam touches the extreme edge of the crystalline ectasia. This scissors movement of the reflexes may be considered pathognomonic of axial lenticonus, and for the first time we have been able clearly to demonstrate this in our case of peripheral lenticonus (Fig. 2).

That posterior lenticonus must be considered a congenital anomaly is confirmed in our case by the association of a whole series of more or less important anomalies: slight microcornea (horizontal corneal diameter of 11 mm. in the right eye and

Vogt,[24] p. 453.

* References 14 and 16.

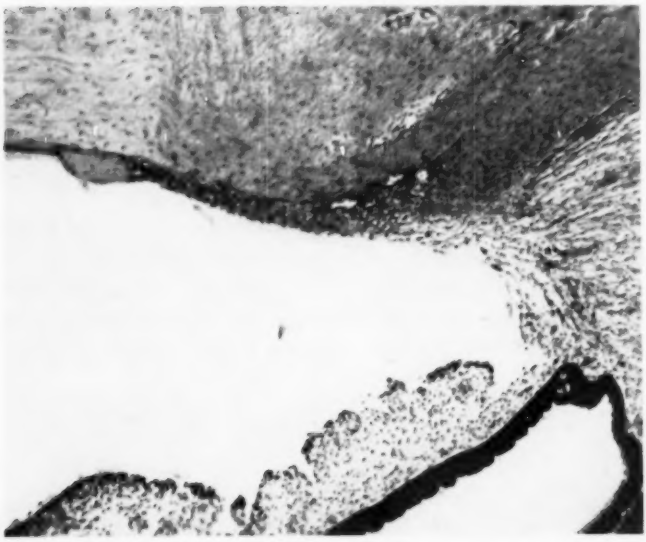

Fig. 3.—Posterior surface of the cornea covered by a membrane ending in a hyaline swelling (marginal dysplasia, or abortive form of Axenfeld's posterior embryotoxon). × 75.

Fig. 4.—Section through the upper peripheral lenticonus, linked to the hypoplastic ciliary body by a tissue formation (degenerated ectopic retina). × 13.

of 12.5 mm. in the left eye), posterior marginal dysplasia of the cornea (abortive form of Axenfeld's posterior embryotoxon), coloboma of the anterior layer of the iris at 8 o'clock, and, finally, peripheral choroidal coloboma in the same quadrant.

Anatomopathological Examination.—In February, 1951, the patient died of abdominal tuberculosis. We received the eyeball, preserved in Zenker's solution, a year and a half after our clinical examination. After having been embedded in celloidin, it was cut into a series of horizontal sections. In spite of some changes due to transportation, the histological sections allowed us to find all of the anomalies noted clinically. On examining these systematically beginning with the

Fig. 5.—Region of the superior eccentric lenticonus. Two layers of an epithelial membrane are covering the lenticonus. Behind, we can distinguish a loose connective veil. × 250.

anterior part of the globe, we found, first of all, the marginal dysplasia (Fig. 3). Starting from the iridocorneal angle, a membrane covers the posterior surface of the cornea to end in a hyaline swelling (abortive form of Axenfeld's posterior embryotoxon).

In the next section, the upper peripheral lenticonus can be seen (Fig. 4), linked on the temporal side to the ciliary body, which, moreover, is hypoplastic at this point, by a tissue formation, the various layers of which suggest a degenerated retina.

Stronger magnification shows that this heterotopic retinal mass is covered on its anterior surface by a layer of pigment, which also coats the posterior surface of the lenticonus. The crystalline capsule is clearly visible at this level. The epithelial membrane covering the lenticonus is formed by the pigmentary layer and by an external layer which is not pigmented, and which corresponds to the epithelium of the ciliary body. This nonpigmented layer covers the posterior surface of the aberrant mass with a marked thickening at this level.

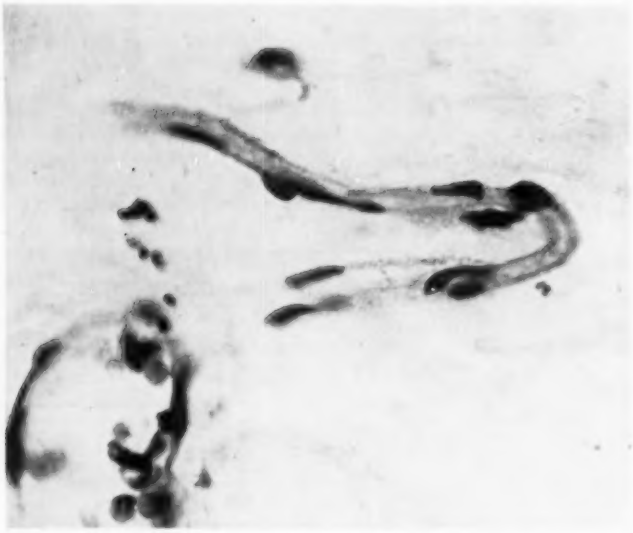

Fig. 6.—Vascular loops of the embryonic type in the loose connective tissue behind the lenticonus. × 588.

Fig. 7.—Lower part of the upper lenticonus: incomplete (mesodermal) coloboma of the iris; hypoplasia of the ciliary body. × 14.

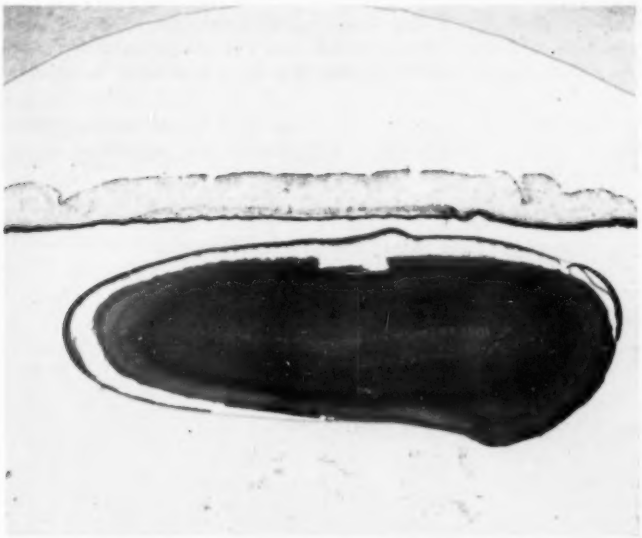

Fig. 8.—Inferior eccentric lenticonus covered by a layer of pigment. × 12.

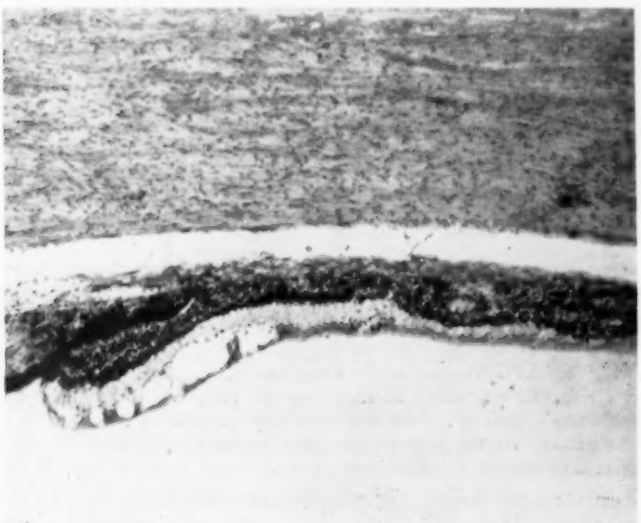

Fig. 9.—Peripheral coloboma of the choroidea. On the left side, pigmentary epithelium coming from the ciliary body is interrupted; retinal fold shows cystoid formations. × 57.6.

With a still stronger magnification, we can see in the next section (Fig. 5) the crystalline epithelium, the capsule, and the two layers of epithelial membrane covering the lenticonus. Behind, we can also distinguish a very loose connective veil with some vascular loops of the embryonic type (Fig. 6). This connective membrane also covers the posterior surface of the aberrant retina. One naturally wonders whether it is not a remnant of the primitive secondary vitreous.

The following section (Fig. 7), at the level of the lower edge of the upper lenticonus, shows an incomplete coloboma of the iris, affecting particularly the mesodermal layers, and hypoplasia of the ciliary body.

In the zone between the two lenticoni the lens is regular in shape and is not covered by any layer of pigment. One can still distinguish the partial coloboma of the iris and the marginal dysplasia, which at this point ends in a small round formation.

Fig. 10. Heterotopic nuclei in the region of the inferior lenticonus. × 110.4.

Corresponding to the clinical picture, the lower lenticonus (Fig. 8) is much less pronounced but is also covered by a layer of pigment.

At this level we also find a malformation of the ciliary retina, connected to the lens only in the lower part of the lenticonus.

The following sections correspond to the lower peripheral region, which clinically had the appearance of a choroidal coloboma. Starting from the periphery (Fig. 9), we note that the pigmentary epithelium is interrupted and that the retina, atrophied at this point, ends in a fold, with cystoid formations. In the posterior part, the pigmentary epithelium reappears, but the retina is still markedly thickened and deformed.

In our case, the association of peripheral posterior lenticoni with numerous congenital malformations obviously suggests a prenatal origin of the crystalline ectasia. We should point out, first of all, that there is neither a rupture of the capsule nor a persistent hyaloid artery, which, according to Hess's classic theory,[4] would permit of an explanation of the pathogenesis of these lenticoni. We naturally wonder whether the epithelial layers covering the two lenticoni may not have played a part in the genesis of the crystalline ectasia.

On examining the lens in the region of the lenticoni with strong magnification, we were struck by the finding at this level of a zone characterized by the presence of numerous nuclei, such as are usually seen only at the level of the equatorial germinative layer. This zone of heterotopic nuclei is seen at the level of the upper lenticonus, as well as at that of the lower, which is covered by a simple layer of pigment (Fig. 10). Taking these findings as a basis, we propose the hypothesis of an exaggerated apposition of crystalline fibers in connection with an aberrant zone of growth; this theory would also explain the ectasia of the lens and, to a certain extent, would justify the idea of Pergens,[13] who considered the lenticonus as a phacoma, although this term is not very well chosen. It would, indeed, seem preferable to speak of a localized hyperplasia of the lens. The fact that the zone of

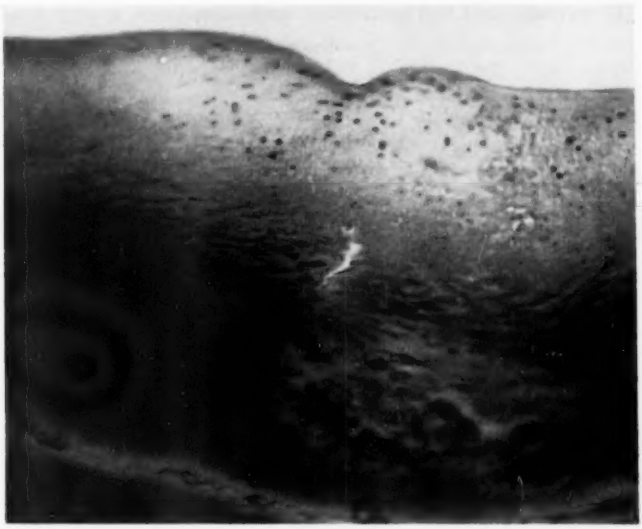

Fig. 11. Heterotopic nuclei in the posterior surface of the lens in the area between the two lenticoni. × 110.4.

heterotopic nuclei is also found in the area between the two lenticoni shows that these crystalline ectasias cannot be attributed simply to the covering of their posterior surface by a layer of pigment (Fig. 11). Two swellings, separated by a small notch, can be seen at this point.

It is evident that these findings, in a case of peripheral lenticoni with multiple malformations, do not of themselves allow us to conclude that there is an analogous process in the formation of the typical axial lenticonus. However, when we do, one day, have the opportunity of examining such a case histologically, we must not forget to pay particular attention to the possible presence of zones of heterotopic nuclei at the level of the posterior pole.

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ELECTRIC RESPONSES OF THE HUMAN VISUAL SYSTEM

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IN RESPONDING to the high distinction of being selected to deliver the Fourth Annual John E. Weeks Memorial Lecture, I have chosen a topic which may seem somewhat remote from the field of endeavor of the man whose memory we are honoring tonight. When John E. Weeks was a forward-looking young man, his keen mind turned to bacteriology, the new and exciting field of his day, with the result that his name has become linked with that of the great Koch. And thus his name is best remembered and known to ophthalmologists the world over. Yet those who were more closely associated with him knew that his curiosity was not limited and that he took a broad interest in the advancement of ophthalmology, a specialty so universal that there is hardly a medical or scientific discipline upon which it does not touch. With this thought in mind I shall talk to you about some of the electric responses of the human visual system.

This is a field which has barely begun to be tilled, and our knowledge is still rudimentary. My discussion will of necessity have to be largely a report on work in progress and the statement of a program. In spite of this I shall have the opportunity to speak only of some points which appear to me to be of particular importance, restricting myself severely to the subject of the title, the response of the human visual system. The vast body of knowledge obtained in animal experimentation will be barely touched upon.

Let me first answer the question, "Why should we be interested in the electric responses of the visual system?"

The study of the visual system can be conducted along two lines. One may study the psychophysiologic aspect of vision, i. e., the subjective responses to changes in one's environment, or one may investigate the objective changes which take place in the visual system as a result of specific stimulus situations. The subjective responses can be studied only in man; in animals they can at the most be inferred by analogy. Objective studies, on the other hand, are severely restricted for methodologic reasons and have in the past remained largely in the province of animal experimentation.

The subjective method of investigation has led to a deep understanding of the visual act in man, and this method will always be of paramount importance to the physiologist and the psychologist, as well as to the practicing clinician. But our curiosity will not rest until we know all there is to know of the anatomic and physiologic mechanisms which underlie the act of vision and form the objective correlative of the subjective responses.

The Fourth Annual John E. Weeks Memorial Lecture.

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It is not only scientific curiosity which impels us to study these objective phenomena. If objective methods were available for the investigation of normal living visual systems, much might be learned which, when compared with the behavior of abnormal visual systems, might give rise to a better understanding of disease processes and eventually point the way to more adequate treatment. And this is, in the last analysis, the most important consideration to us as physicians.

Foremost among the objective phenomena which can be observed in living animals and in man in response to visual stimulation are the electric phenomena exhibited by all parts of the visual system. In man, the only responses which can be recorded at the present time are the responses of the retina to light by means of electroretinography, and such responses of the visual cortex as may be recorded through electroencephalography.

ELECTRIC RESPONSES OF RETINA

The fact that the eyes of animals exhibit a so-called resting potential as well as changes in potential upon illumination has been known to physiologists for a long time, and by 1911 the essentials of the electric response of the retina to light were known. But intensive and extensive detail studies became possible only after the introduction of modern means of amplification and recording.* Human electroretinograms were recorded as early as 1876 and then again in the 1920's; yet only recently has the technique of human electroretinography become sufficiently simplified to allow a wider study of physiologic phenomena in man and the application of this method to clinical problems.†

In the eyes of animals and man there exists a so-called resting potential between the electropositive cornea and the electronegative back of the eye, so that a current in an external circuit flows from the cornea to the posterior pole of the eye. This resting potential is of such magnitude that it may be recorded by placing one electrode on the cornea, and the other on the frontal or temporal region, the corneal electrode being always positive.

Upon illumination of the eye, changes in this resting potential are recorded. The result is a polyphasic retinal action current known as the electroretinogram. The typical sequence of events in the electroretinogram of all vertebrates is as follows: The first effect to appear is a slight negative deflection of short duration, the a-wave, which is followed by a sudden large increase in positivity of the cornea (the b-wave, or b-potential). After its decline a slow large positive swing, the c-wave, appears if the stimulus light is of sufficiently long duration. With strong, prolonged stimulation, especially in light-adapted eyes, a final positive deflection (the d-wave, or "off" effect) occurs on cessation of illumination.

Considering the complexity of the retinal structure, the complexity of the electroretinogram which represents the algebraic sum of the a-, b-, and c-potentials is not surprising. From the study of the electroretinogram it has been concluded that it can be analyzed into three components. These were named by Granit [2] PI, PII, and PIII. PI represents the partial process which is responsible for the c-wave; PII is the process which results in the positive b-wave, and PIII is the negative component which in its first uncompensated part produces the a-waves,

* References 1 through 3.

† References 4 and 5.

but swings positive to the base line, as the illumination ceases, just prior to the time PII swings downward to it, thus causing the appearance of the d-wave.

That PI, PII, and PIII are independent variables was proved with pharmacologic methods by Granit,[2] who showed that these processes could be selectively influenced by drugs, and also showed that PI is the first to disappear in ether anesthesia and that PII and, finally, also PIII are obliterated only with increasing depth of anesthesia. This greater resistance of PIII over PII may prove to be of definite ophthalmologic interest.

Of the three partial processes which make up the ERG, the b-wave is the only one known to lead to discharge in the optic nerve and is, therefore, thought to be the only one which contributes directly to visual function. This makes it of particular importance in ophthalmologic considerations.

Our knowledge is as yet not sufficiently advanced to permit a definite assignment of the components of the electroretinogram to the activity of specific retinal elements, but tentative assumptions have been made. Granit [2] believes that the process causing the b-potential is localized in the synaptic layers of the retina, and Bartley [6] has suggested that it might be specifically localized in the bipolar cells. Bartley also feels that there is much evidence to show that the a-wave may be due to the reaction of the receptor cells. We are entirely in the dark as to the origin of the c-wave, although this process is known to be absent from the electroretinogram of pure cone retinas.

Neither is it as yet clear how the components of the electroretinogram are related to the activity of the rods and cones. It is, however, evident that the negative potentials are closely associated with cone activity, while the b-wave is more closely associated with the activity of the rods, although it is not exclusively linked with them. Evidence for these assumptions is found in the differences existing between the electroretinogram of light- and that of dark-adapted eyes and in some clinical cases.

The electroretinogram of the light-adapted eye differs materially from that of the dark-adapted eye, and these differences will be discussed presently. However, I wish first to point out that the parameters of the stimulus—its intensity, size, duration, location on the retina, frequency, and wave length—have in every case a decisive influence upon the form which the electroretinogram assumes, i. e., upon the prevalence of its various components and upon their time relationships.

Because of this it is important to know the details of the technique employed in the recording of an electroretinogram. In general three elements are required for this purpose: electrodes for the derivation of the action current of the eye, an amplification and recording system, and a device for the stimulation of the eye with light.

The electrodes represent a major technical problem. Riggs,[7] and later Karpe,[4] pioneered the solution of this problem in human electroretinography by introducing contact lens electrodes. Mr. Lee Allen and I have devised, together, a corneal speculum electrode [8] which consists of a plastic speculum to which a corneal contact lens is attached by a wire spring. Near the edge of this lens a circular silver wire is recessed into the plastic. The silver makes contact with the cornea through a film of methylcellulose. This electrode has many advantages and has proved eminently satisfactory, especially for routine clinical investigations.

For amplification and recording I have employed a standard Grass ink-writing electroencephalograph. The use of an ink-writer makes it readily possible to combine electroencephalography with electroretinography, and is adequate for most purposes. Only for special studies may oscillographic recording be required.

Most important with regard to the results obtained is the apparatus for the light stimulation of the eye, since, as I have pointed out, the form of the electroretinogram depends upon the parameters of the stimulating light. This also requires that standard conditions be observed to achieve comparable results in clinical electroretinography.

If one employs, as in the conditions which Karpe [4] laid down, a light stimulus of 20 to 80 lux and of 1/25 second's duration, with a frequency of one stimulus every 15 seconds, after five minutes of dark adaptation, an electroretinogram is registered

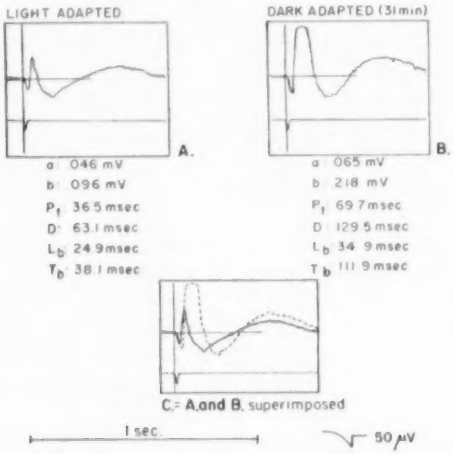

Fig. 1.—Comparison of electroretinograms obtained from light- and dark-adapted eye of one observer: (*a*) amplitude of a-potential; (*b*) amplitude of b-potential; (P_t) culmination time of b-wave; (D) total duration of electroretinogram; (L_b) latency of b-potential; (T_b) duration of b-wave.

from which the a-wave and c-wave are absent and which consists essentially of a b-wave with an average amplitude of 0.35 mv. and a duration of 0.15 second. This conscious simplification has been very helpful in establishing certain basic characteristics presented by the electroretinogram in diseased conditions of the eyes, since the b-wave appears to be the best expression of the sensitivity of the retina and is alone associated with the impulse response in the optic nerve. Nevertheless, it is recognized that for a deeper insight it is necessary to vary the parameters of the stimulus.

The light source which I have employed in the last three years in the study of the electroretinogram consists of a high-intensity stroboscopic light source, controlled electronically by two devices, one for single flashes, the other for repeated flashes. The duration of the flashes is very brief (30 msec.) and essentially independent of the frequency. Intensity and wave length can be controlled with neutral or colored filters. The details of the arrangement of the apparatus and the condi-

tions of the experiments have previously been described.[5] It suffices to say here that the stimulus conditions differ from those of Karpe's standard conditions in that the stimulus is very intense but also very brief. It is impossible at present with my arrangement to change the duration of the stimulus, but we have a new device in the developmental stage which should allow accurately graded variations of intensity, duration, size, and location of the stimulus within a very wide range and which will, of course, also permit the use of light of different wave lengths.

The electroretinograms which were obtained by the method described have confirmed previous findings regarding the difference in the electroretinogram of light- and dark-adapted eyes (Fig. 1), except insofar as they are modified by the

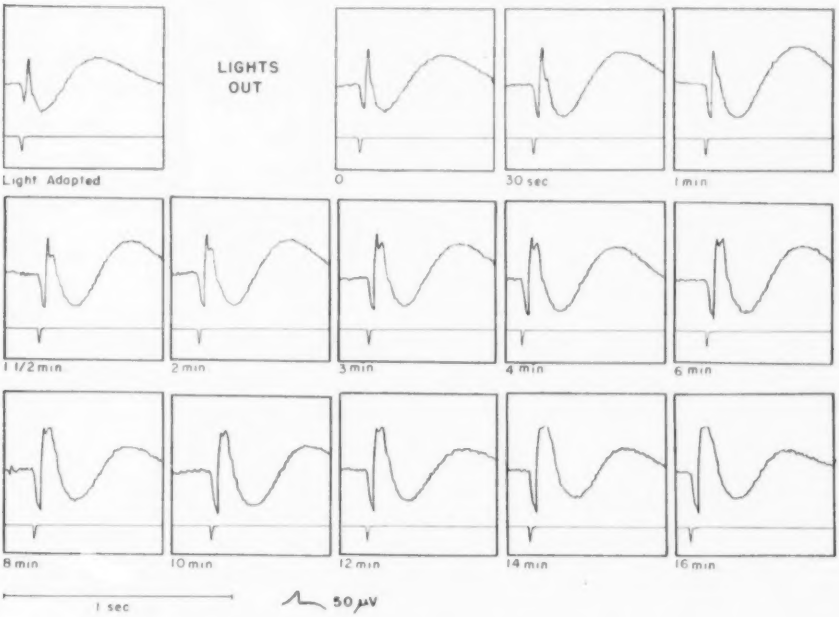

Fig. 2.—Successive electroretinograms of observer R. L. with increasing dark adaptation. Increasing prominence of "scotopic" spike on descending branch of b-wave.

very intense, brief light stimulus used. Generally speaking, the electroretinogram of the human light-adapted eye showed a relatively large a-wave and a relatively small b-wave. The duration of the b-wave is much shorter than in the dark-adapted eye. In the latter the a-wave is obliterated to a larger or smaller extent, depending on the intensity of the stimulus; the b-wave is two to five times higher in amplitude, its duration much longer, its rise and fall less steep than in the light-adapted eye. In that eye the b-wave resembles a low, sharp peak; in the dark-adapted eye it assumes the form of an elevation with a plateau.

These differences are explained when recordings are made with different intensities of light flashes and at different times during the course of dark adaptation. Adrian [6] has shown that the b-wave of the human electroretinogram can be

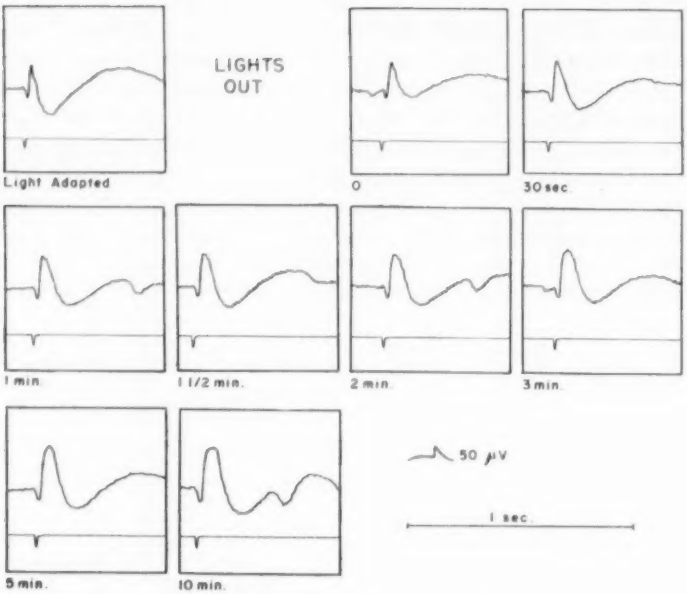

Fig. 3.—Successive electroretinograms of observer M. H. with increasing dark adaptation.

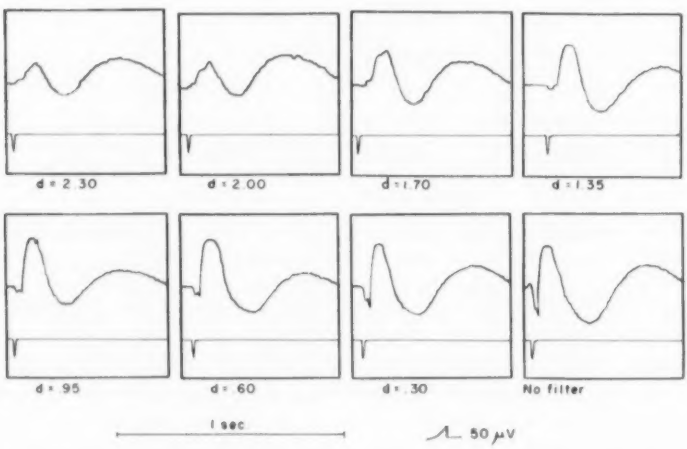

Fig. 4.—Electroretinograms obtained from dark-adapted observer with stimuli of increasing intensity.

divided into a rapid and a slow component, the former being present in the light-adapted eye, the latter being more prominent after dark adaptation. Adrian considers the rapid component to be related to the photopic mechanism, the slower component to the scotopic. The correctness of this view has been confirmed from the beginning in my electroretinographic studies. Figure 2 indicates plainly the relationship of these two phases in progressive dark adaptation. In the light-adapted state there

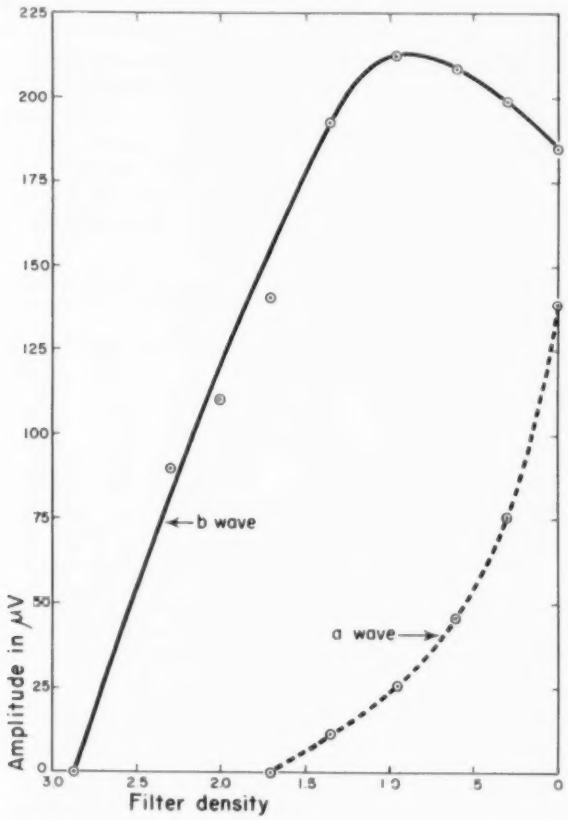

Fig. 5.—Amplitudes of a- and b-waves of dark-adapted eye resulting from stimuli of increasing intensity (the data plotted are taken from the electroretinograms shown in Figure 4). The absence of an a-wave at lower stimulus intensities, the maximum in the amplitudes of the b-waves, and the steady increase of the a-wave with increasing intensity are evidence that the b-potential is more closely connected with rod activity, the a-potential with cone activity.

is to be noted in the majority of the recordings a small spike on the descending branch of the b-wave, which I attribute to the scotopic component. This spike becomes more prominent during the first two or three minutes of dark adaptation; it increases in height and finally determines the whole character of the electroretinogram, whose duration also steadily increases as dark adaptation progresses. Not all subjects show the two phases equally clearly. In some the process is much

more rapid and the scotopic electroretinogram is fully established after a few minutes (Fig. 3); subsequent changes relate only to an increase in amplitude of the b-wave and in the duration of the electroretinogram. One of the problems with which we are at present concerned is an attempt to correlate these individual differences in the behavior of the electroretinogram with individual differences in the behavior of dark adaptation.

The fact that the relationship of the scotopic and photopic components of the electroretinogram is so clearly demonstrated must be attributed to the very high intensity of our light source. If the intensity is reduced, the scotopic component is isolated; if the intensity is increased, the photopic component becomes increasingly apparent also in dark-adapted eyes. This is demonstrated in Figure 4, which reproduces the results of an experiment in which the eye of a normal observer was stimulated successively with flashes of nine different intensity levels, beginning with the lowest intensity. At the initial intensity no electroretinogram was recorded. With the succeeding three intensities there was no a-wave noted in the record; the a-wave appeared at the fifth and increased up to the maximum level. There was

Characteristics of the Electroretinogram with Light Flashes of Different Levels of Intensity

Neutral Filter (Density)	a-Wave, in mv	b-Wave, in mv	b / a	Peak Time of b-Wave, in msec.	Duration of ERG, in msec.	Peak Time of b-Wave, in % of Duration
2.78	.....	.....	....	...	...	..
2.30	.....	0.090	....	133	194	68
2.00	.....	0.111	....	131	187	70
1.70	.....	0.146	....	124	181	68
1.35	0.012	0.193	16.8	109	163	61
0.95	0.026	0.213	8.2	89	161	56
0.60	0.046	0.208	4.4	81	154	53
0.30	0.076	0.198	2.6	73	142	51
No filter	0.138	0.180	1.3	65	142	46

also an increment in the amplitude of the b-wave, but with the seventh level of intensity the amplitude of the b-wave began again to decrease, because of the greater prominence of the photopic component with the brighter flashes (Fig. 5). The steady increase of this component was also expressed by the fact that the peak time of the b-wave represented almost 70% of the total duration of the electroretinogram at the lowest effective intensity levels, whereas it made up only 46% of the total time at the highest intensity (Table).

Another interesting observation, which will only briefly be mentioned here and which is at present being studied in some detail, is the hitherto unobserved phenomenon that the electroretinogram recorded after cessation of prolonged dark adaptation becomes more or less "negative"; that is, there is at first no elevation above the base line. It consists then of a negative deflection, the a-wave, and a small photopic component which only after some minutes rises above the base line and remains depressed for a remarkably long time (Fig. 6). This phenomenon has been noted in all records. The return to the initial normal values is speeded up by prolonged stimulation of the eye with bright light.

The relative prominence of the photopic and scotopic components of the electroretinogram is also brought out in records in which the frequency of the flashes is varied. I have reported previously [8] that the amplitude of the b-wave decreases

as the frequency of the flashes increases. At the same time the scotopic component becomes less and less pronounced (Fig. 7). With a speed of one stimulus per second, electroretinograms differ little from those recorded at longer intervals. With two stimuli per second the second flash produces a typical light-adapted, though subnormal, electroretinogram; with three stimuli per second there are three such light-adapted electroretinograms, etc. After a few flashes there establishes itself with all frequencies a type of electroretinogram which is characteristic of the particular level of adaptation produced by the frequency used. With increasing frequency these successive electroretinograms appear not only smaller; their shape approaches more and more that of the electroretinogram obtained in light-adapted eyes, and the increasing prevalence of the photopic component is well observed. It will be mentioned here only in passing that the recording of electroretinograms

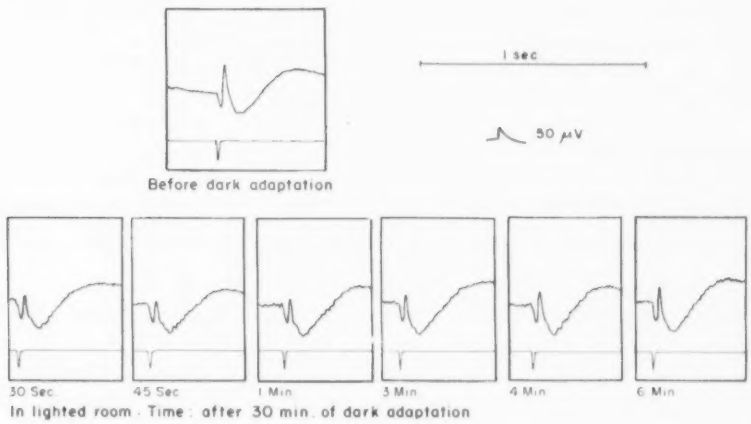

Fig. 6.—Effect of diffuse illumination of room on electric response of previously dark-adapted eye. Upper tracing: eye light-adapted prior to dark adaptation. Lower tracings: six electroretinograms recorded in brightly lit room after 30 minutes of dark adaptation.

with different stimulus frequencies is also of interest in connection with the study of flicker fusion frequency.‡

Further support for the view that the b-wave contains a photopic and a scotopic component is found in the observation of Monnier,[14] confirmed by Vukovich,[15] that the electroretinogram obtained on stimulation of the retinal periphery has a "scotopic" form, even with high intensity of the stimulating light, and in the comparison of the electroretinograms of a patient with hemeralopia (Schubert and Bornschein [16]) and of a patient with achromatopsia (Vukovich [15]). In the former the electroretinogram is extinguished with lower stimulus intensities and with higher stimulus intensities it has a "negative" form, very similar to that which I have just described as occurring after prolonged dark adaptation. The patient with achromatopsia, on the contrary, showed a subnormal electroretinogram of the "scotopic," or "peripheral," type. Similar observations have been made on a number of patients in our electroretinographic laboratory and will be reported by George

‡ References 2, 8, and 10 through 13.

W. Bounds Jr. and Bruno Bagolini. These findings, as well as those obtained with colored filters (Adrian [9]) point the way toward electroretinographic tests of macular function which we do not as yet possess.

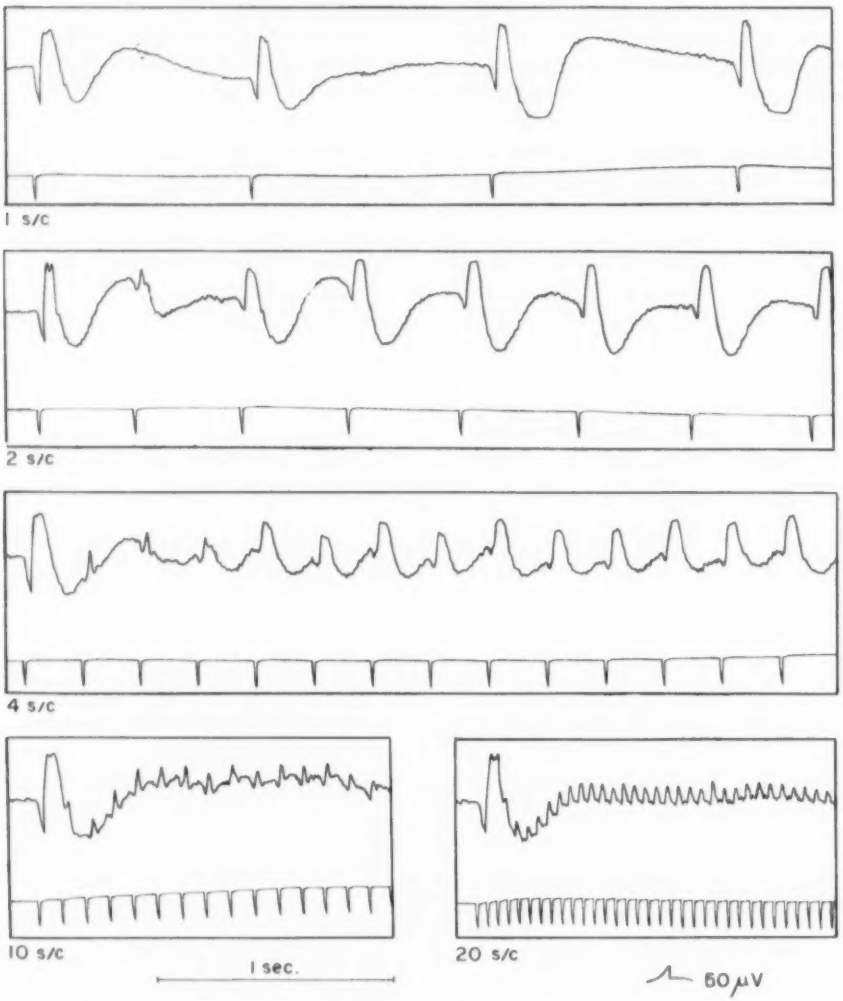

Fig. 7.—Electroretinograms obtained from dark-adapted observer with stimuli of increasing frequency.

Of major ophthalmologic interest is the fact that the electroretinogram is highly sensitive to the oxygen supply. Granit [2] has found that interference with circulation or respiration may lead in the cat to a selective removal of the b-wave. Noell [17] and Bornschein and Zwiauer [18] did not note in the rabbit a greater resistance of the a-wave than of the b-wave to anoxia, but Noell observed that in the cat and in the

monkey the b-wave disappeared before there was any measurable reduction of the a-wave. Man would seem to behave more like the animals in the latter group. In man the compression of the eyeball leads—after a short initial increase—to a reduction of the b-wave to zero, while the reduction in the a-wave is less pronounced.[8] Also, there is a remarkable increase in the size of the a-wave after the release of the pressure over what it was prior to compression. From the standpoint of sensory physiology it is significant that the visual sensation disappears while there is still a relatively large b-wave present, and that there is a considerable increase in the culmination time of the b-wave and in the total duration of the electroretinogram.

From the clinical standpoint the application of the compression test would appear to be of some interest in patients with glaucoma, since it has been shown [8] that the loss in b-potential is greater in glaucomatous eyes than in normal eyes. Patients with circulatory disturbances of the retina should also be studied by this test, since the findings of Henkes [19] reported in a series of excellent papers on electroretinography in circulatory disturbances of the retina would indicate that the alterations found are due to deficiencies in the blood supply, and consequently in the oxygen supply of the retina.

In connection with the survival and early reappearance of the a-wave in the compression experiments, it is worth noting the behavior of a patient wtih traumatic retinal detachment whose reattached retina gave, one month after surgery, a subnormal electroretinogram insofar as the b-potential was concerned, but a relatively high a-wave, which was of the same magnitude as the b-wave.[8]

ELECTRIC RESPONSES OF OPTIC NERVE, VISUAL PATHWAY, AND VISUAL CORTEX

For all their importance, the electric responses of the retina—even if they were fully understood—can tell only part of the story. They can tell only how the impulses are generated which travel through optic nerve and visual pathways up to the visual cortex and beyond to produce those final reactions to which the visual impressions in man's consciousness correspond.

Thus far the direct study of the electric events in the visual pathways has been carried out only in animals, and I shall very briefly summarize some salient points of the results obtained.

When the retina is stimulated by a light of constant intensity, the optic nerve responds—after a latent period—with impulses of high frequency. If the stimulation is continued for a few seconds, the frequency decreases as the cells of the sensory epithelium adapt. Unlike all other nerves from sense organs, the optic nerve shows an "off" response after cessation of the stimulation, again following a latent period. All this has been shown clearly by Adrian and Matthews [20] on the eye of the eel. These authors have also found that the frequency of discharge is proportional to the intensity of the stimulating light and to the size of the stimulated retinal area.

Comparing the electric responses of the optic nerve with the electroretinogram, it is found that there is a time interval between the onset of the a-wave in the electroretinogram and the onset of the initial high-frequency discharge in the optic nerve. The "off" effect is also represented in both the electroretinogram and the recordings from the optic nerve. The correspondence between the two may be even closer. Bartley [21] has reported that the initial "on" response in the optic nerve to a flash

of medium intensity is a double one. The first may be due to the response of the cones, the second to that of the rods (Brazier [22]), just as there is a photopic and scotopic component in the retinal action current.

The impulses arising in the optic nerve are carried to the lateral geniculate body and through the optic radiation to the visual cortex. Not all the fibers contained in the optic nerve are directly concerned with the act of vision. Only the set of fibers of larger diameter, having a conduction rate of 60 meters per second, synapses in the geniculate body; the set of finer fibers (conduction rate 25 meters per second) goes through to the superior colliculus without synapsing.

The next way-station is the synapse of the thalamocortical fibers with the cells in the internal granular layer of the visual cortex. The axons of these cells radiate in many directions. This offers great difficulties for the interpretation of their electric signals. Nevertheless, Bishop and his school, in their extensive studies in animals, have been able to identify discrete components in the cortical response to photic stimulation and to assign them to the optic radiation and the lower, middle, and upper cortex, respectively. They achieved this by placing electrodes at different depths into the cerebral substance. Among these components, a long-lasting surface-positive deflection, most prominent in the superficial electrodes, is considered to be the main cortical response to stimulation of the optic nerve (Bishop and O'Leary [23]).

In man we have only the information given us by electroencephalography. But the investigation of the human electroencephalogram has led to two observations which are of considerable interest. One is the disappearance of the alpha rhythm, the other the phenomenon of photic driving.

The outstanding component in the electroencephalogram of the adult is a spontaneous rhythmic activity with a frequency of 8 to 13 cps and an average voltage of about 30 μv. This rhythm, which is most conspicuous in the parieto-occipital region, has been termed the alpha rhythm. The origin of this dominant frequency of the electroencephalogram is still in doubt, although various theories have been emitted to account for the fact that the numerous cells necessary to produce the voltages in question are so coordinated as to discharge in unison rather than at random. A particularly interesting observation with regard to the alpha waves is the attenuation or disappearance of this rhythmic activity, which is noted when the subject opens his eyes or when the eyes are stimulated by light. It tends, however, to return to some extent when the stimulus persists. This whole behavior leads one to suspect that there is a close relationship between alpha activity and visual sense, although, as Brazier [22] points out, this relationship lies in the visual association areas rather than in the primary visual areas.

The situation is further complicated by the fact that blocking of the alpha rhythm occurs also on opening of the eyes in a completely darkened room and on any alerting of the subject. In spite of these complexities, the alpha blocking offers interesting possibilities from the standpoint of the ophthalmologist.

Before discussing these, a second remarkable feature of the electroencephalogram, the so-called photic driving, should be mentioned. Photic driving consists of rhythmic potentials evoked in the occipital cortex by repetitive stimulation of the eyes with light. Within limits, these potentials have the same frequency range as the stimulating flicker. Not every subject shows this response equally clearly. In some it can be detected barely—or not at all—by visual inspection of the records.

Adrian and Matthews,[24] who discovered the phenomenon, thought that it represented driving of the alpha rhythm beyond its normal spontaneous rate, but Adrian offered later [25] the alternative theory that the driving response and the alpha rhythm compete, i. e., that they do not coexist. However, Daly [26] has concluded from his observations that these two entities do coexist, and in a study of patients with amblyopia ex anopsia conducted by C. Wesley Watson and myself [27] it was found that photic driving was often combined with alpha activity when the stimulation was restricted to the amblyopic eye, but not when the normal eye was exposed to the flicker.

From the ophthalmologic standpoint, it is significant to note that Watson [27] believes fixation and accommodation to be of primary importance for the production of a driving response. Various workers have indeed observed a marked decrease in amplitude when fixation was shifted only a few degrees to one side of the center of the stimulating light. Daly,[26] who has confirmed this perimetric effect, points to the possibility that it may be more apparent than real and may be due to the fact that the cortical representation of the peripheral fields is buried within the mesial surfaces of the occipital lobes, whereas the macular area is represented in the occipital pole, and is thus closer to the electrodes.

Photic driving can also be obtained when the subject's eyes are closed. This is generally recognized and is somewhat in contradiction to the perimetric effects just described. Daly [26] has carefully analyzed the influence of eye closure and has come to the conclusion that it affects the driving response variously in different subjects: It may decrease it, augment it, or leave it unchanged. The situation is further complicated by the fact that changes in amplitude with closure of the eyes occur in some persons only at certain frequencies. As yet there is no satisfactory explanation for these divergences.

The question now arises, "How can electroencephalographic methods be applied to ophthalmologic problems, and what may be expected from them?" The answer must come from actual investigations, and until now only a modest beginning has been made in this direction. Since both alpha-blocking and photic driving depend upon stimulation of the eyes, the condition of the eyes and the condition of the visual pathways must materially influence both these entities. Investigation of the cortical responses should be conducted in normal observers under various conditions of stimulation and the result applied to patients with abnormal conditions of the retina, as well as of the optic pathways. The combination of electroretinography and electroencephalography offers a particular promising approach.

Thus far the few scattered reports in the literature are not conclusive. Baudouin and associates [28] noted an alpha rhythm of low amplitude in a patient with bilateral blindness. Their findings in four patients with hemianopsias and in one with central scotoma were contradictory. According to Case,[29] patients with hemianopic defects and involvement of the optic radiations always show a significant difference in the alpha waves recorded from the two hemispheres. Levinsohn and associates [30] investigated the electroretinogram in a large number of children and found anomalies in the tracings from the occipital lobes to be much more frequent in children with strabismus than in normal children. Kluyskens [31] has attempted to utilize alpha blocking as a means of objective perimetry and has found that the same small stimulus will be more effective in depressing alpha activity when applied to the retinal center than when applied to the retinal periphery. He has also found that

blocking of the alpha rhythm will occur only if the stimulus is perceived. He believes that this method lends itself to the objective investigation of the field of vision of normal subjects, as well as of patients with restrictions of the visual field due to organic lesions.

In contrast to Callahan and Redlich,[32] who did not note characteristic changes in patients with amblyopia ex anopsia, Watson and I [27] found that the alpha rhythm was more easily suppressed when the amblyopic eye was stimulated than when light was flashed into the dominant eye. We also found that photic driving was less easily produced through stimulation of the amblyopic eye; when it occurred, it was less regular, appeared often momentarily, and was of lower voltage. It is of interest to compare with this the report of Cornil and Gastaut,[33] who claim to have encountered a decided hemispheric dominance in the electroencephalogram of the majority of otherwise normal right- or left-handed subjects. The dominant hemisphere showed alpha waves of smaller amplitude than the other hemisphere; the blocking of the alpha rhythm was more complete on the dominant side, and rhythmic responses to repetitive light flashes were induced with greater ease on that side than on the other. Cornil and Gastaut explained this by a facilitation of the conduction of impulses toward the dominant hemisphere as compared with the nondominant.

The application of electroencephalographic methods to ophthalmologic problems has only just begun. Many questions are opening up, some of which are now under study by our group in Iowa City. To learn more about photic driving, the influence of intensity and area of stimulus, fixation, accommodation, and wave length is being studied. The questions of laterality of response and of possible differences between monocular and binocular stimulation are being investigated. Answers to these questions are necessary before definite conclusions can be drawn from recordings obtained from patients with anomalies of the eyes and of the visual pathways.

Another line of inquiry to be pursued is into the behavior of the alpha rhythm in bilaterally blind people, particularly in correlation with age at onset and duration of the blindness. The development of the alpha rhythm in children raises particularly intriguing problems. It is known that waking occipital rhythms are absent during the first three months of life. When occipital rhythms first occur, they are very slow (3 to 4 per second); they increase in rate, at first rapidly, then more gradually, until at about 13 years of age the adult range of alpha frequencies is established. If something were known about the development of the alpha rhythm in children blind from early infancy due to an ocular cause, an idea might be formed to what extent functioning eyes are necessary for the functional development of the visual pathways. And this, as is well known, is a problem which crops up time and again in discussions of the etiology of neuromuscular anomalies of the eyes.

The investigation of the time relationship between the stimulus, on the one hand, and the primary evoked response or the blocking of the alpha rhythm, on the other, may be of help in solving both physiologic and pathologic problems. Since the time elapsed from the onset of the stimulus to the first reaction detectable in the electroencephalogram includes the time consumed by retinal processes, this latter time must be deducted in assessing the condition of the optic pathways. This can be achieved by combining electroretinography with electroencephalography, a method developed particularly by Monnier and his associates. By deducting the latency of the b-potential in the electroretinogram from the blocking time of the alpha rhythm, Monnier and Boehm [34] found a retinocortical time of 185 ± 6 msec.

Applying this technique to a patient with bilateral partial tabetic optic nerve atrophy, Monnier and Jeanneret [35] found that the retinocortical time was markedly increased in this instance (229 msec. on the right side and 264 msec. on the left side).

The large spread of the figures for the retinocortical time is in part due to the difficulty of determining the precise moment at which the alpha rhythm has ceased. Monnier [36] has, therefore, adopted the latency of the primary evoked occipital rhythm as criterion of cortical response. If it was present, this response occurred in normal people at 120 ± 15 msec. following the stimulus. By deducting from this the latency of the retinal b-potential (70 msec.), Monnier obtained a central transmission time of 50 ± 15 msec. In my own investigations I have used the peak time of the retinal b-potential and deducted this from the peak time of the primary evoked cortical response and have found in a series of normal observers with a stimulus frequency of four stimuli per second an average central transmission time of 115 ± 15 msec. From Daly's investigation,[26] it is likely that the latency of the primary evoked response, investigated with appropriate methods, actually shows a shorter latency than was hitherto assumed and that the figures will have to be revised in the future.

I have taken you on a long and, I fear, rather arduous journey. It is my hope that I may have aroused in some of you an interest in what appears to me to be the fascinating problem of the relationship between the happenings in the nervous substratum of the visual system and the act of vision. Some of the matters which I have discussed may seem strictly academic today. I feel sure that many of them will be turned to practical clinical use tomorrow.

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COMPARISON OF SCLERAL RESECTION AND SCLERAL FOLDING IN EXPERIMENTAL SHORTENING OF THE EYE

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BUFFALO

SHORTENING of the eyeball by scleral resection has proved to be successful in many cases of retinal detachment in which diathermy either has failed or offers a poor prognosis. Such cases include detachments in aphakic eyes without visible tears, total detachments, cases with exceptionally large tears, and detachments with fixed star folds or vitreous strands. Müller * was the first to perform the scleral resection operation for retinal detachment in 1903, but Lindner † deserves the credit of reviving and advocating the idea of Müller in 1933. He elaborated a new, precise technique and defined the cases in which success could be expected. Since then many authors have reported results achieved by this operation, among them Pischel and Miller,[7] Pischel,[8] Bogart,[9] Vail,[10] Borley,[11] and Hughes.[12]

Because certain hazards and complications are encountered in scleral resection, Lindner suggested in 1933 [3] a method of scleral folding to obtain the desirable shortening of the globe. He performed the operation in six cases in 1946,‡ but he later found that he had not obtained a permanent shortening of the eyeball.§

Since pathological material of human eyes was lacking, the histological changes responsible for the beneficial effect of scleral resection for retinal detachment were not known. It was logical, therefore, to seek information from experimental work on dogs' eyes.[13] On the basis of the experience obtained from this work, I developed in 1949 a technique of scleral folding which provides the same permanent shortening of the eye as the scleral resection, but without displaying the hazards and complications encountered with the latter.‖

Since that time reports of authors (Friemann,[16] Paufique and Hugonnier,[17] Shapland [18]) using modified techniques of scleral folding indicate that the two operations, scleral resection and scleral folding, have similar effects in selected cases of retinal detachment.

TECHNIQUE

My experimental studies were carried out in two groups. Lindner's method of scleral resection was done on 26 normal dogs' eyes.[13] In each case a strip of sclera 3 mm. wide and 30 to 33 mm. long was excised 9 to 10 mm. posterior to the limbus

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at the equator of the globe. In preliminary experiments, Lindner's preplaced absorbable surgical (gut) mattress sutures (Fig. 1) had proved unsatisfactory for holding the wound tight; so I used nonabsorbable (silk) sutures with intrascleral bites 2.5 to 3.0 mm. wide (Fig. 2). The final resection of the scleral strip under the preplaced sutures was especially difficult in dogs' eyes because of the hemorrhages from the intrascleral venous plexus. A medium-sized forceps with two additional hooks (Fig. 3) was devised for better manipulation of the preplaced sutures (Fig. 4) during this step.

In the second series of operations performed on 12 dogs' eyes, shortening of the globe was achieved by folding the sclera according to a method which I reported in 1950.[14] After a band-shaped strip of sclera of the same size and location as that in scleral resection had been outlined, the outer two-thirds of the sclera was excised. The remaining third of the sclera (here specifically called "scleral lamella") was left as thin as possible, because the thinner it is, the less tension there is in the wound, and therefore the tendency of the sclera to unfold is diminished. Ten to 12 silk mattress sutures were then placed in the same way as in scleral resection (Fig. 2), special care being taken to insert them intrasclerally about 3 mm. beyond each scleral wound lip. After the intraocular tension had been lowered by tapping the anterior chamber, the sutures were tightened and knotted in sequence. In this way the scleral wound lips were brought together, while the "scleral lamella" bulged inward spontaneously.

The surgically treated eyes of both groups were enucleated at times varying from several hours up to three months after operation, and the specimens were examined histologically.

COMPARISON OF PROCEDURES

A. Operation.—The operation of scleral folding is technically less complicated and shorter than that of scleral resection, for the following reasons:

1. The choroid protected by the "scleral lamella" is never exposed during the operation; consequently, no injury or rupture of this membrane is possible.

2. The sutures are placed after the outer scleral strip is removed, and the complicated dissection of the scleral strip with scissors under the preplaced sutures is avoided.

3. The operation can be interrupted at any time without any detriment to the eye, as the choroid never lies exposed.

4. Hemorrhages in the eyes of dogs are less frequent and less severe during scleral folding than in scleral resection.

In scleral folding, the proper insertion of the mattress silk sutures, as indicated above, is very important, because they are exposed to higher tension than in scleral resection. The presence of the "scleral lamella" produces a tendency of the sclera to unfold, for merely mechanical reasons, and the postoperative intraocular tension is considerably higher because the scleral capsule remains intact and thus no fluid from the inner eye leaks out, as in scleral resection.

Histological evidence of the considerable intraocular pressure is the presence of marked hyaline degeneration of the scleral fibers around the sutures 5 to 10 days after scleral folding (Fig. 10). This tissue damage is due to the intense pressure which the threads exert upon the sclera. In scleral resection only traces of similar changes were observed.

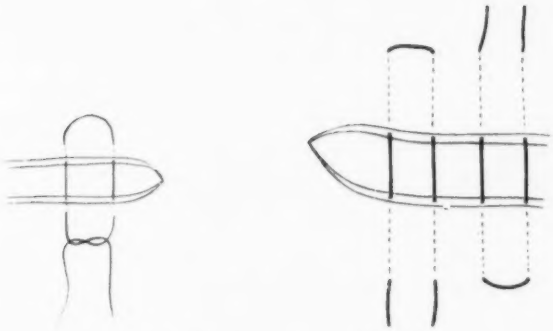

Fig. 1.—Mattress suture of Lindner.

Fig. 2.—The silk threads are inserted at a width of about 3 mm. beyond each scleral wound rim. The knot comes to lay alternately once at the posterior and once at the anterior wound rim.

Fig. 3.—The forceps with the special hooks.

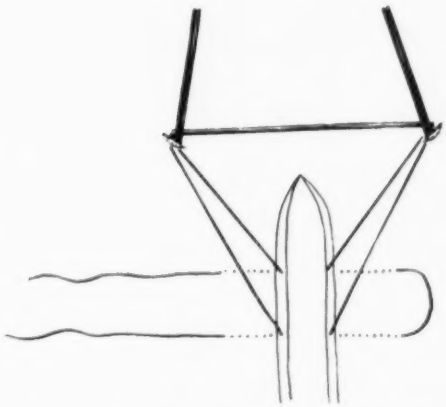

Fig. 4.—The loop of the U-shaped suture can be stretched and moved in any desirable direction during the definite resection of the scleral strip.

B. Ophthalmoscopical Findings.—The ophthalmoscopical findings are the same in scleral folding and scleral resection. Immediately after either operation, a band-shaped protrusion of the choroid and retina is observed along the operation area. In both cases the bulging of the choroid disappears in three to four days after the operation. The protrusion of the retina flattens more slowly in scleral resection, but about eight days later no ophthalmoscopically visible changes are seen in the operation area. However, in scleral folding 10 days after the operation a thin, transparent retinal fold along the operation area is still visible. This difference is due to the fact that reattachment of the retina occurs earlier in scleral resection than in scleral folding.

C. Histological Findings.—Sclerotic: After scleral resection considerable tissue swelling, hyperemia, and inflammatory cells appear in the sclera around the wound, reaching their peak 48 to 72 hours after operation and subsiding slowly 3 to 4 days later. In scleral folding there are few postoperative inflammatory changes within the wound. However, in both operations the scleral wound is firmly closed by connective tissue within about 10 days.

In scleral resection the connective tissue proliferation accomplishing the closure of the scleral wound can start from the choroid, the episcleral tissue, or the sclerotic itself. According to the histological findings, the connective tissue proliferation starts mainly from the choroid; the episcleral tissue participates little, while the sclerotic itself contributes to a slighter extent in this process.

In scleral folding, the choroid cannot participate in the connective tissue formation since the "scleral lamella" lies between the choroid and the scleral wound. This has to be, and is, satisfactorily accomplished by the episcleral tissue and the sclerotic alone.

In any case, after the two operations there is no difference in the histological structure of the wound area when cicatrization is completed. Three weeks after the operation, the connective tissue closing the wound can hardly be distinguished from the surrounding sclera. Another scleral resection or scleral folding within the same area could easily be accomplished.

The band-shaped protrusion of the "scleral lamella" (Fig. 6) on the inner surface of the sclerotic after scleral folding diminishes soon after operation and disappears within a relatively short time (Fig. 7). Ten days after the operation no remarkable unevenness of the inner surface of the sclera exists (Fig. 10); therefore, in this respect no essential difference exists between the two operations.

Choroid: In both operations, it is obvious that the shortening of the sclerotic creates a surplus of choroid and retinal tissue in normal eyes. In scleral resection the choroid develops folds along the excised scleral strip, compensating for its tissue surplus (Fig. 5). These folds generally last two to four days. In scleral folding the choroid is first indented by the "scleral lamella" toward the interior of the eye (Fig. 6), but, during the operation or immediately after, the choroid detaches from the sclerotic and takes its normal stretched shape, compensating for its tissue surplus by a histologically visible thickening, extending to the posterior pole of the globe. In no case does the choroid develop folds in scleral folding.

After scleral resection, thickening of the choroid, with marked hyperemia and heavy infiltration with leucocytes, appears several hours after the operation. The inflammatory changes reach their peak 48 hours after the operation, extending almost to the posterior pole of the globe, and subside very abruptly within 2 to 3

days, so that 14 days after the operation generally no more inflammatory signs are found. As a result, after that time more or less firm adhesions are seen between the choroid and the inner surface of the sclera around the wound. Similar heavy inflammatory changes occur in the adjacent ciliary body, leading to notable cicatrization of that structure and its epithelium in one-third of the cases.

Fig. 5.—The operation area of a normal dog eye immediately after scleral resection. Note the well-adapted wound rims of the sclerotic. Over the wound are the folded choroid and the detached and folded retina.

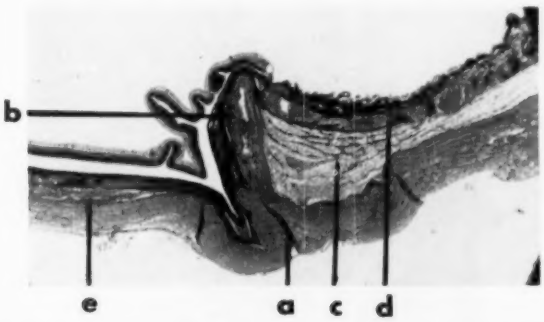

Fig. 6.—The operation area immediately after the scleral folding operation: (*a*) well-adapted scleral wound; (*b*) the folded "scleral lamella" bulging toward the interior of the globe and indenting the choroid and the retina; (*c*) blood and serum between the sclerotic and the hyperemic ciliary body (*d*); (*e*) blood between the sclerotic and the choroid posterior to the scleral wound. Detachment and folding of the retina.

Essentially different is the response of the uvea to the scleral folding operation. Neither the choroid nor the ciliary body shows noticeable inflammatory changes; especially are there no permanent tissue alterations.

The prompt stretching of the choroid within the operation area in scleral folding is caused by the presence of the "scleral lamella," which detaches it from the inner surface of the sclera, and the absence of almost any inflammatory changes in the choroid. The normal elasticity of the latter structure is thus maintained, and adhesions to the scleral wound are prevented by the "scleral lamella."

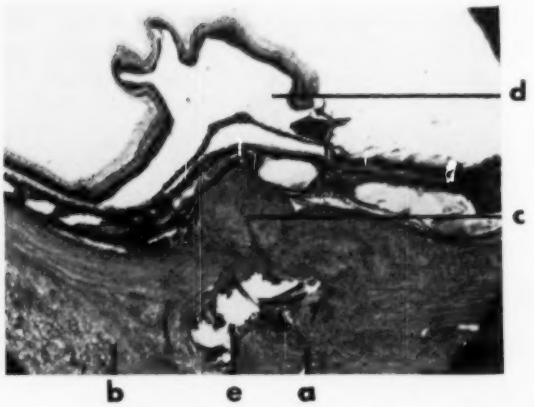

Fig. 7.—Operation area five days after the scleral folding operation: (*a*) well-adapted scleral wound rims; (*b*) episcleral tissue; (*c*) the "scleral lamella" compressed and considerably smaller than immediately after the operation; (*d*) subretinal fluid; (*e*) remnants of a silk thread. The retina is detached; the choroid does not show folds.

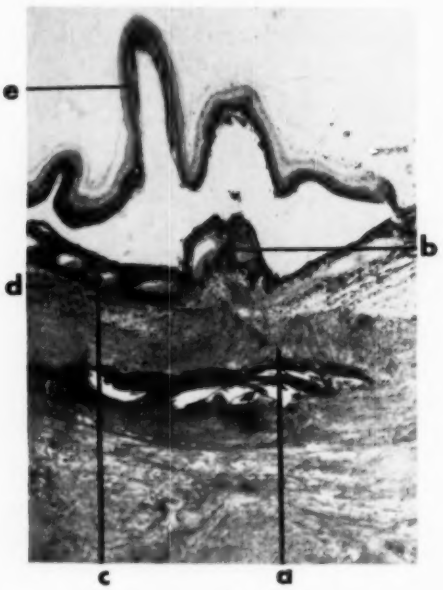

Fig. 8.—Operation area five days after the scleral resection operation: (*a*) loose connective tissue closing the scleral wound; (*b*) thickened choroid, with remnants of the folds which form immediately after the operation; (*c*) thickened choroid; (*d*) subscleral hemorrhage. Detached and folded retina; partial destruction of the outer nuclear layer (*e*) due to mechanical damage by the operation. This results in several empty spaces in this layer.

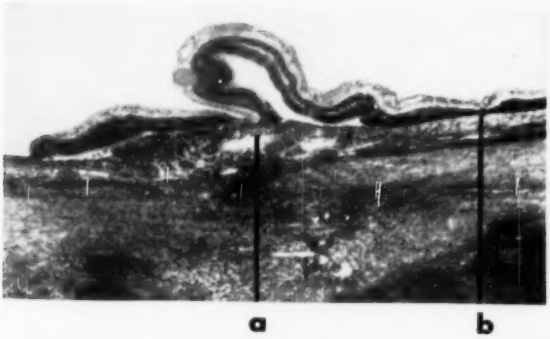

Fig. 9.—Operation area 10 days after scleral resection, with considerable infiltration of the wound area with leucocytes and lymphocytes. The retinal fold is fixed by adhesions (*a*, *b*) between retina and choroid; after scleral resection the reattachment of the retina in the operation area is very firm. The scleral wound is closed.

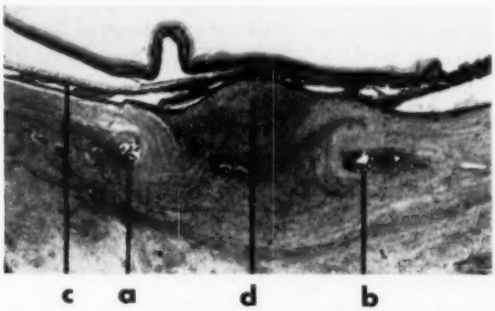

Fig. 10.—Operation area 10 days after scleral folding: (*a*, *b*) silk threads surrounded by hyaline degenerated scleral fibers; (*c*) tapetum lucidum. The folded "scleral lamella" has almost disappeared and only a slight protrusion is still seen (*d*); the stretched choroid. Loose reattachment of the retina in the operation area. Between the two silk threads is the closed scleral wound.

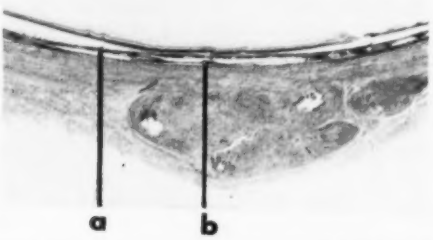

Fig. 11.—The operation area three months after scleral folding. Encapsulated collections of granulation tissue around silk threads. The site of the previous scleral wound cannot be distinguished from the normal sclerotic. Normal choroid. The retina is reattached to the choroid, with slight rippling of the retina (*a*, *b*). By this the tissue surplus in the operation area is compensated to some extent.

Suprachoroidal Space: After the scleral resection, a considerable amount of serum and blood is found subsclerally, causing the entire ciliary body and the whole choroid to be detached from the sclerotic. The fluid should be considered as an exudate because it contains a great amount of albumin and blood; obviously, it is the result of the postoperative inflammatory changes of the uvea and the sclera that follow this operation.

In scleral folding very small amounts of blood and serum were found subsclerally, owing to the negligible inflammatory signs of the uvea and the sclerotic.

Retina: After both operations, owing to surplus tissue, the retina is detached from the pigment epithelium within the operation area and develops folds (Figs. 5 and 6). Thus, an artificial band-shaped separation along the operative field is produced. From the anatomical point of view, it is similar to the serous retinal detachment in man. I have previously demonstrated [14] that this detachment develops during the operation and is caused by purely mechanical processes, especially the surplus of retinal tissue following the shortening of the scleral capsule.

The sudden detachment and folding of the retina causes mechanical damages to the retinal structure within the operation area. They are similar after the two operations, but are considerably less after scleral folding. Necrosis of many cells of the outer nuclear layer constitutes the most important of these damages (Fig. 8). This is followed by a general shrinking of the retina within the operation area, resulting in a diminution of the retinal tissue and providing favorable space conditions for reattachment of the retina, as both retina and sclera have become smaller. In scleral resection the detached retina closely readheres to the pigment epithelium within 10 to 14 days after operation (Fig. 9). In scleral folding the detached retina, in spite of the fact that it will approach the pigment epithelium sooner, may remain flatly detached for several weeks but will finally become permanently reattached. In both operations the surplus retinal tissue in the operation area is reduced by the general shrinkage following the cell necrosis and the formation of small circular folds, of various sizes. In scleral resection some of the larger folds become fixed, this being due to the close and rapid reattachment of the retina with the inflamed choroid (Fig. 9). In scleral folding, because of the absence of significant inflammatory changes in the choroid, the folds always stretch and decrease to a multiple slight wrinkling of the retina (Fig. 11).

After scleral folding the connection between the reattached retina and the pigment epithelium is a very loose one, in contradistinction to the condition after scleral resection, in which the connection between the reattached retina and the pigment epithelium proves histologically to be very firm. This difference is obviously due to the inflammatory changes of the choroid and the sclerotic after scleral resection, for the mechanical shortening of the globe, as well as the remaining factors, is the same in the two operations.

SUMMARY AND CONCLUSIONS

An identical permanent shortening of the normal dog's eye can be achieved either by scleral resection or by scleral folding.

Both operations produce an artificial separation of the retina along the operation area. Reattachment of the retina is more rapid and considerably firmer after scleral resection, this being due to significant inflammatory changes of the uvea and sclera.

After scleral folding, prompt and reliable tissue relaxation of the choroid occurs, extending from the wound to the posterior pole of the globe.

With regard to the pathology of the human eye, the following conclusions may be drawn:

1. The anatomical conditions in human eyes are more favorable than in dogs' eyes for both operations. The sclerotic is considerably thicker, and almost no intrascleral vessels exist. Therefore, either operation can be performed with success in human eyes when the proper technique is employed.

2. The anatomical relations of the three membranes of the eye (sclerotic, choroid, and retina) are, in both normal human eyes and normal dogs' eyes, the same at the equator. It is logical to conclude that both operations performed on normal human eyes will cause the same artificial band-shaped separation of the retina seen in dogs' eyes. Therefore, in cases of serous retinal detachment in man, scleral resection or scleral folding should be avoided in areas with attached retina.

3. When the surgeon wants to achieve shortening of a normal eye or a prompt and reliable relaxation of the choroid, as, for instance, in high myopia, scleral folding should be performed.

4. When shortening of the eyeball has to be performed for treatment of retinal detachment, the scleral resection must be advocated. Histological examination on experimental scleral resection shows that reattachment of the retina occurs more promptly and more firmly than in scleral folding, this being caused by the considerable inflammatory changes of the choroid in scleral resection.

5. It is reasonable to assume that scleral folding combined with artificial inflammation of the choroid would have the same effects in treatment of retinal detachment as the scleral resection. The artificial inflammation can be produced either by the injection of chemical substances between the sclerotic and the choroid or by diathermic coagulation. The latter is to be preferred, as it can be applied to any specific area and in whatever strength required. Ten to 15 perforating applications with a 1.8 to 2.0 mm. needle placed between the U-shaped sutures at a distance of 2.5 mm. beyond the posterior scleral wound lip should be the most favorable method.[16] Such coagulates would not interfere with the proper scleral wound closure. It would not be advisable to apply diathermy or chemical agents to the "scleral lamella" or near the scleral wound lips, because this would damage the scleral tissue and interfere with the rapid and firm closure of the scleral wound. Postoperative unfolding of the sclerotic would be possible if this were done.

In view of the histological findings described here, one would be justified in assuming that the favorable clinical effect of scleral resection or scleral folding combined with artificial inflammation for certain types of retinal detachment is due to the mechanical shortening of the eyeball and an extensive mild inflammation of the choroid. The shortening of the scleral capsule, together with the suprachoroidal exudation, brings the choroid nearer to the detached retina, and the extensive inflammatory changes of the choroid result in the reattachment of the retina.

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J. F. Bergmann, publisher of *von Graefes Archiv für Ophthalmologie*, permitted the use of Figures 3, 4, 6, and 8 to 11.

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EXPERIMENTAL FUNDAL LESIONS

A Method and Observations

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ONE OF the important features of drug evaluation in ophthalmology is the experimental creation of lesions in animals which are standard, reproducible, and similar in location and appearance to those found in humans. With few exceptions,* studies of bacterial lesions and tumor transplants have been confined to the anterior segment. In contrast, a large number of conditions begin in or are confined to the posterior segment in humans. The present study has been done to show the potentialities of the posterior segment as a source of experimental lesions and to demonstrate a method of producing them.

The fundus of the rabbit eye is particularly accessible because of the soft orbital wall and the ease with which the eye can be proptosed painlessly. It has previously been shown † that the suprachoroidal space of the rabbit is readily separated from the sclera. It was felt that various fluids could be injected into the demonstrated potential space, and a procedure of injection was developed, which is reported as follows:

I. SUPRACHOROIDAL INJECTION

The pupils of adult mongrel pigmented and albino rabbits are dilated with 1 drop of 1% atropine and 10% phenylephrine (Neo-Synephrine) hydrochloride one-half hour prior to being used. The animal is placed in a special box (Fig. 1) which supports it comfortably and firmly. One per cent tetracaine (Pontocaine) hydrochloride on an applicator is touched to the conjunctiva of the superior cul-de-sac, avoiding the cornea, in each eye and a retrobulbar injection of 0.5 cc. of 1% procaine hydrochloride is made through the anesthesized area. Since the manipulation is one which must be done while constantly observing the fundus, the operator uses his most facile hand for manipulating the point of the needle into the suprachoroidal space and holds the ophthalmoscope with the other, as in Figure 2. The box is turned so that the eye which is to receive the choroidal injection is uppermost, and the eye is then proptosed by the assistant. Proptosis makes the posterior pole more accessible and steadies the eye against the push of the needle as it pierces the sclera. The needle is introduced into the retrobulbar space, hugging the sclera as it is slipped posteriorly, and is guided so as to avoid the superior rectus muscle. The presence of the needle and its position is seen as a ridge appearing in the fundus, and in albino rabbits a metallic sheen is readily detected. The point of the needle can be thought of as a tiny spatula, and the aim of the operator is to insert it, bevel up, between the sclera and the choroid. There is a resistance when the point of the needle engages the outer layers of the sclera, and it is maintained as the needle is pushed through into the supra-

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Presented in part at the Annual Wills Eye Hospital Conference, March 21, 1953, by Adolph W. Vogel, M.D., and Irving H. Leopold, M.D.

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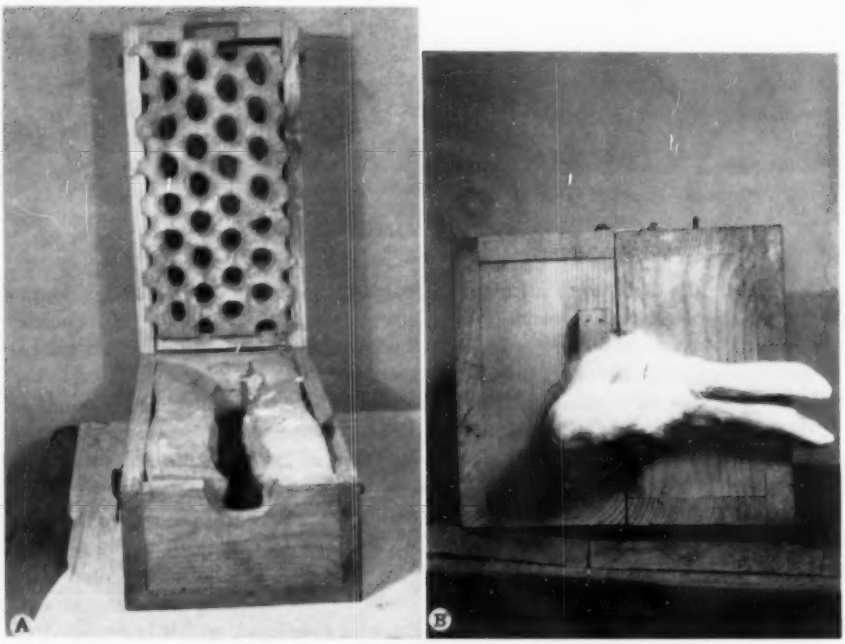

Fig. 1.—*A*, special box, lined with sponge to hold rabbits. *B*, box closed.

Fig. 2.—The operator holds the syringe in his most facile hand and observes progress of needle point into the suprachoroidal space, with constant ophthalmoscopic observation.

choroidal space. As the point is slowly introduced, the choroid and retina can be seen rising up with the pressure, the choroidal vessels blanching completely as they are compressed. The assistant increases or decreases the proptosing pressure with the squint hook according to the instructions from the operator. When a clear, bright, undiminished gleam from the tip of the needle is seen, the bevel is made to lie parallel with the choroidal layer, and the needle is pushed so that the entire bevel and the distal 1 mm. of the shaft is within the suprachoroidal space. The needle is now in position for the injection. The assistant releases all pressure except that needed to keep the eye from sinking back into the orbit, and the plunger of the needle is pushed. A momentary resistance is felt, then there is a sudden give, and the choroid and retina are lifted in bleb-like manner around the needle, so that its contour is not visible. The suprachoroidal space can accept 0.005 cc. of fluid without regurgitation along the shaft of the needle. Since it is impossible for the operator to look at the gradations on the barrel of the tuberculin syringe at the time of injection, the assistant can tell him the amount of fluid being injected. This, however, is not completely accurate, as there are variations in the amount of resistance felt to the plunger and amounts as small as 0.005 cc. are difficult to gauge. It was therefore necessary to design a syringe‡ (Fig. 3) which would deliver repeatedly precise minute amounts of fluid, without the necessity of the operator watching the gradations. This permits complete concentration on the positioning of the needle in the suprachoroidal space and its maintenance while the solution is injected. After the desired amount is delivered, the needle is withdrawn and the eye allowed to settle back into the orbit. Twenty-four hours after the injection there

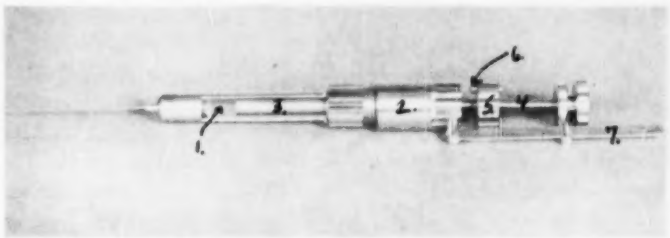

Fig. 3.—A tuberculin syringe barrel (*1*) is inside the housing (*2*), and a stainless steel piston (*3*) has been tooled to fit it exactly and the pressure tested. The upper one-half of the piston has been threaded 1/45 in. (*4*). One counterclockwise turn of the stop (*5*) is equivalent to a forward movement of one 0.01 cc. gradation on the tuberculin syringe. By using a "bullet-nose" stop (*6*) which clicks into four countersunk holes in the housing, quarter turns can be made, and amounts as small as 0.0025, 0.0050, 0.0075, and 0.01 cc. can be accurately and repeatedly injected. Tap water from these settings has been weighed on the analytical balance and found to check.

The knife bar (*7*) prevents slippage of the piston when the syringe is being loaded and handled. The stop is turned the desired amount, and after the needle is placed in position, the plunger can be blindly pushed and delivers the exact amount of fluid.

is a slight conjunctival engorgement in the superior cul-de-sac. There has been no loss of animals from the procedure. Once the technique is learned, it should be possible to inject six eyes an hour. The rabbit eye turns on its axis as it is proptosed, so that the fundal area lying about 1 D. D. below the nerve head is almost invariably the site of the injection.

Results

India Ink.—In order to localize the position and distribution of the fluid, India ink was first injected in a minute amount which ophthalmoscopically appeared as a tiny, black, well-demarcated area about 1 D. D. below the nerve head. A larger injection, of 0.02 cc., of ink was made in the left eye of an albino rabbit. A dramatic picture ensued, in which black fluid spurted from the needle to the extreme

‡ Mr. Charles Gobel, of the University of Pennsylvania School of Chemical Engineering, is responsible for a large part of the design of the syringe.

periphery, through the entire lower half of the fundus and the lower one-fourth of the upper fundus. The fundal reflex of this eye became black immediately, making a startling contrast with the natural red reflex of the right eye. Twenty-four hours later all media were clear, and they have remained clear for six months. The ophthalmoscopic picture was one of an irregular pattern of well-circumscribed connected islands and branches of black pigment lying deep in the fundus. In one month it could be seen that the central part of the deposit was clearing and assuming a silvery-gray sheen, while the periphery of the deposit remained deep-black. By the fourth month the choroidal vessels within the pools of India ink had been surrounded by migrating India ink particles, outlining them more heavily and giving a linear appearance to the deposit. This tendency of the India ink particles to align themselves with the choroidal vessels is similar to the appearance of the pigment migration seen in retinitis pigmentosa. After seven months the vessels were even more prominent, and they seemed to stand out more distinctly as the India ink migrated from between the vessels to their walls.

Beryllium.—It has been shown that granulomas of the skin and osteogenic sarcoma can be caused by beryllium compounds.[12] The possible reaction of pure beryllium on the choroid was investigated by injecting a suspension of minute particles of pure beryllium (20 mg. in 1.0 cc. of 1:5,000 benzalkonium [Zepharin] chloride) into the suprachoroidal space in both eyes of one albino and one pigmented rabbit. Twenty-four hours after the injection numerous bright, shining metallic particles could be seen lying in the inferior half of the fundus. These were more prominent in the pigmented rabbit because of the dark background of the fundus. In the albino rabbit between 50 and 100 small bits of metal were counted. In the pigmented rabbit eyes between 25 and 50 minute metallic particles were seen lying deep in the fundus. These were observed for a period of four months in the albino and two weeks in the pigmented rabbit. The particles remained in approximately the same position and did not cause any apparent reaction in the choroidal vessels or in the overlying media.

Tubercle Bacilli.—By a turbidometric method, suspensions of 200 bacilli per high-power field were prepared, and eight eyes were injected subchoroidally with each suspension. The reaction which followed assumed a generally consistent pattern, and the following description would apply, with minor variations, to all the successful takes. Immediately following the injection, there was a slight fullness of the choroidal vessels, which disappeared in several days. The media remained clear, and the fundus was normal until the 10th to the 14th day, when distinct interference with the vessel markings could be seen, with some haziness of the overlying vitreous, usually confined to or near the area at the site of the injection. The obscuration of detail gradually increased to form a localized grayish, smooth, elevated, well-circumscribed area, usually with normal fundal markings adjoining and clear media overlying. The surface of the lesion was frequently roughened or powdery. In several eyes there were smaller foci of involvement lying below the larger infiltration and within areas of clear fundus details. After several days, the well-demarcated edges became blurred, and there were often finger-like extensions along the retinal surface. Serous, billowing retinal detachments developed, sometimes with elevation of the retinal vessels seen previously.[13]

Up to this stage the anterior chamber shows no reaction other than a faint beam, and there is no ciliary injection. If allowed to progress, the infection spreads to become a panophthalmitis, with marked beam, flare, and fibrin in the anterior chamber. Nodules appear on the iris; the vitreous is cloudy, and all fundal details are obscured. Tension is increased, and perforation will occur. The severity of the lesions and their similarity seem to depend on individual resistance factors.

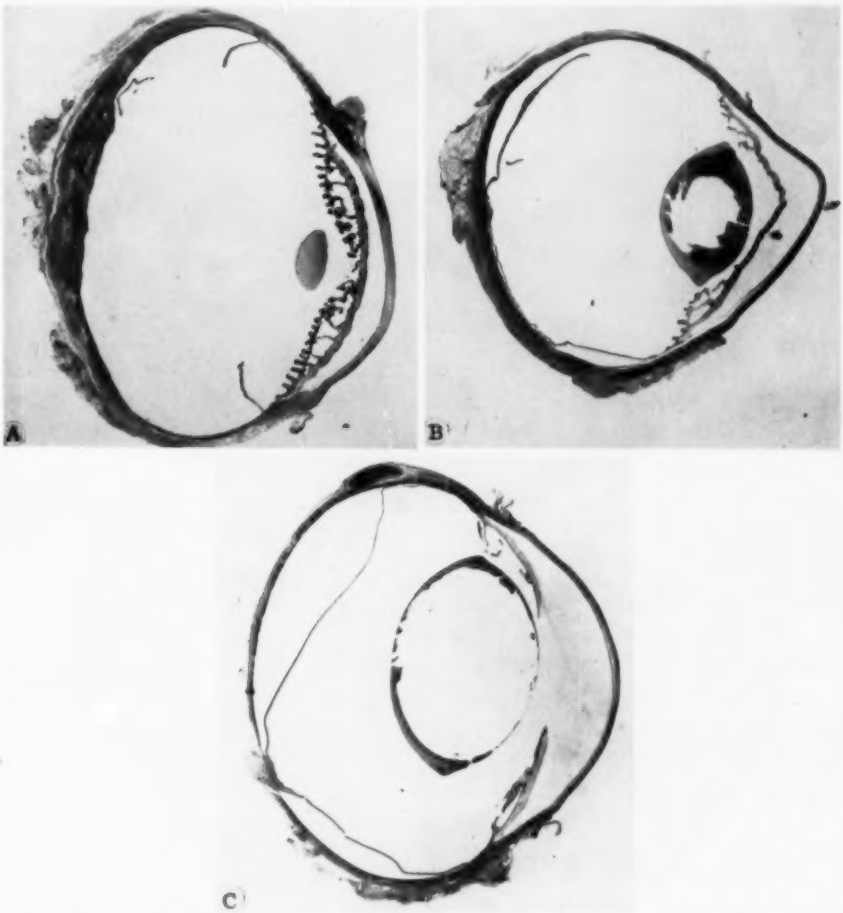

Fig. 4.—*A*, tuberculous choroiditis confined to the fundus but spread beyond the equator, almost touching the ciliary body.

B, marked choroiditis following suprachoroidal injection of 200 bovine tubercle bacilli per high-power field.

C, large episcleral infiltration with choroiditis extending back to the nerve head.

Figure 4 *A* shows the marked tuberculous infiltration of the choroid in the posterior segment and the clear, uninvolved anterior segment. In this eye the infiltration had not spread beyond the equator. Figure 4 *B* shows another eye, in which

the infiltration has spread beyond the equator and almost touches the ciliary body. There are massive choroiditis with elevation of the retina and aggregations of lymphocytes and polymorphonuclears, suggestive of an early granulomatous reaction. Figure 4 *C* shows the process breaking through the sclera and a large episcleral nodular infiltration. Choroidal infiltration can be seen extending posteriorly

Fig. 5.—*A*, higher magnification of the area showing marked infiltration and beginning nodular foci in Figure 4 *C*.

B, choroiditis extending through a large portion of the fundus with relatively little involvement of the overlying retinal structures, indicating rapidity of spread of the tubercle bacillus.

to the nerve head, and the anterior chamber in this case, again, is unaffected. Figure 5 *A* shows a higher magnification of the marked infiltration, nodular foci, disintegrations of retinal elements, and dilated choroidal vessels of the involved area in Figure 4 *C*. Figure 5 *B* shows the choroiditis spread evenly through a large segment of the fundus with preservation of the overlying retinal structure, indicat-

ing the rapidity of travel of the tubercle bacilli. There is episcleral reaction, with many polymorphonuclears in the loose connective tissue overlying the involved portions of the globe.

The multiplication of tubercle bacteria, as shown by the acid-fast stain, was prodigious, and random counts of oil-immersion fields averaged 100 to 150 bacilli. The bacteria were present in the same great numbers throughout the confines of the infiltrative process.

Carcinoma.—Malignant tissue, V-2 strain of rabbit squamous-cell carcinoma, was obtained.§ A suspension which could pass through a No. 21 needle was made by forcing viable tumor tissue through a sieve and adding saline to make a 1:3 suspension. The injection was carried out as described, and fundus examinations were done at two-day intervals. The usual transient hyperemia of the choroid was

Fig. 6.—Drawing of the ophthalmoscopic picture of a V-2 squamous-cell carcinoma of the rabbit choroid.

observed for several days, followed by a clear period of normal fundus markings for five to seven days, when a grayish-white infiltration appeared at the injection site. The area was usually poorly circumscribed, and there was gradual extension inferiorly. Twenty-four to 48 hours after the first sign of activity a large solid mass appeared, rising steeply out of the fundus, with clear media showing every detail of the surface and with borders which were more clearly defined than in the early stages (Fig. 6).

The summit and the superior border were covered with a rumpled, silk-like veil, which lay in or on the retina. Hemorrhagic petechiae could be seen in the tumor, and the entire surface was stippled with tiny nodules, which seemed to be discrete. Figure 7 shows cross sections of two eyes with a typical V-2 squamous-cell carcinoma in the choroid. Figure 8 shows a higher magnification of two areas of

§ Dale C. Coman, M.D., Department of Pathology, University of Pennsylvania School of Medicine.

the fundal tumor. The tumor has invaded and replaced the choroid, lifting up the pigmented epithelium and Bruch's membrane. Early necrosis of the center of the tumor is characteristic of the V-2 carcinoma in any location in the body, and this proves to hold true for the choroid of the eye. If allowed to progress, the mass will perforate the retina and fill the vitreous, giving a white reflex within three weeks.

Lichtgrün.—Both eyes of an albino rabbit were injected subchoroidally to form a pool of *Lichtgrün* of 3 disc diameters in the fundus. The dye was completely absorbed by the fourth day. There was no reaction other than that found after injection of isotonic sodium chloride solution.

Staphylococci.—Subchoroidal injection of 0.005 cc. of a solution of staphylococci (1,000,000 organisms per cubic centimeter as determined by the turbidometric method) was made into both eyes of two albino rabbits. In general, the reactions in all four eyes on the second day showed marked dilation and engorgement of the

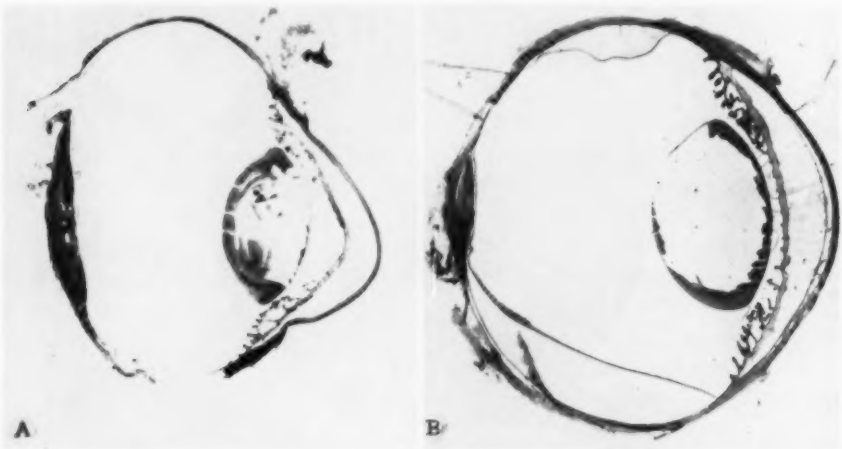

Fig. 7.—Cross sections of two eyes with V-2 squamous-cell carcinoma of the choroid.

choroidal vessels with interruption of the wall continuity in the general area of the injection site by areas of diapedesis. There was a faint beam with the slit lamp. The engorgement and dilation reached its height at the end of one week and then gradually decreased, so that by the end of three weeks there was mild blurring of vascular detail and a few small unabsorbed hemorrhages in the choroid.

Horse Serum.—Four rabbits, two pigmented and two white, were sensitized with horse serum, 10 cc., given subcutaneously. Ten days later suprachoroidal injections of 0.01 cc. of horse serum were done. The reactions following were mild in appearance and contrasted greatly with the marked posterior and anterior segment changes found in intravitreal injections of horse serum into the sensitized animal.[18] In general, there was mild to marked engorgement within 24 to 48 hours of the choroidal vessels, with apparent breakdown of the integrity of the vessel wall in some places, or enough diapedesis and exudate occurred within the choroid to obscure vessel details in small areas at the site of the injection. The choroidal disturbance cleared completely in 9 to 10 days, leaving an ophthalmoscopically normal

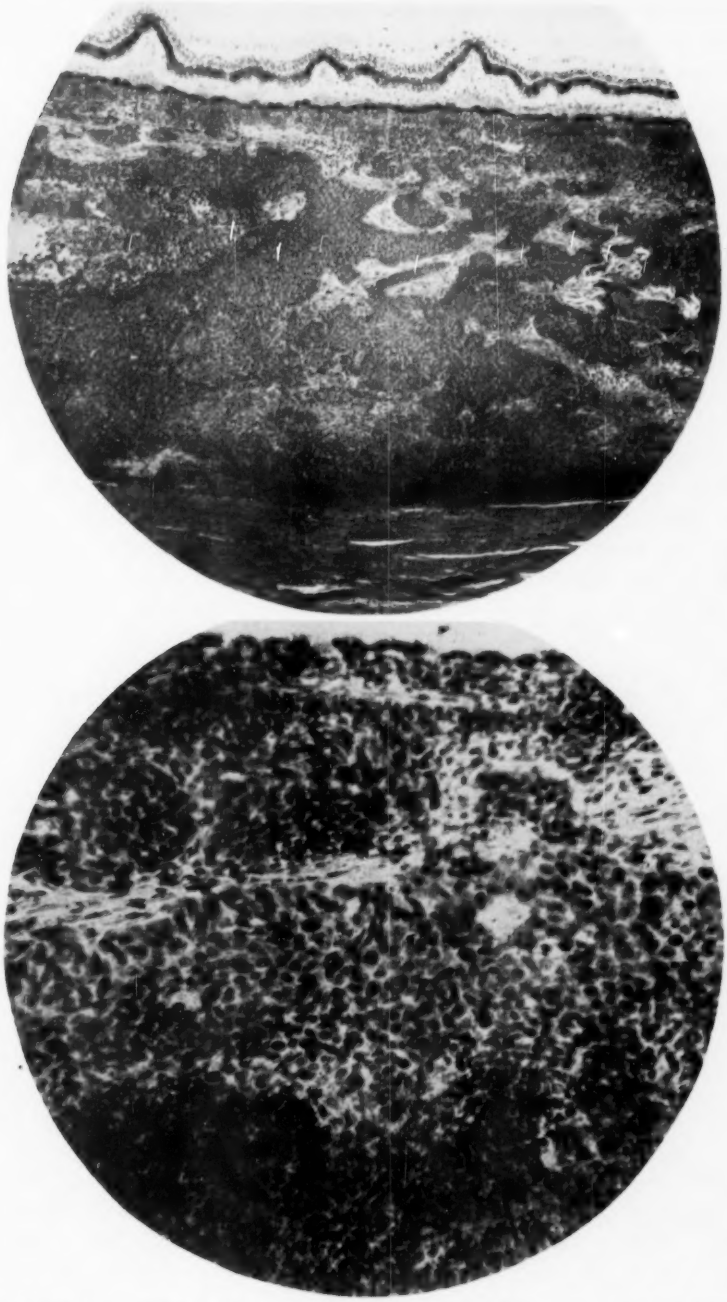

Fig. 8.—Higher magnification of choroidal squamous-cell carcinoma. Note the beginning area of central necrosis.

fundus. The vessels in pigmented fundi of the colored rabbits did not seem to react as much as those of the albino rabbits. This may have been due to masking of detail by the retinal pigment. In two pigmented eyes there was a pigmentary disturbance, consisting of migration and outlining of the needle tract in excess of that found after pure trauma from a needle inserted into the suprachoroid.

Alloxan.—Alloxan injected into the anterior chamber will cause within 7 to 10 days a standard capillary invasion of the cornea.[14] Alloxan, 0.01 cc. of a 0.3 M solution, was injected into the suprachoroidal space in two albino rabbits. There was no evidence of vascular growth or fundal disturbance after a period of two weeks, and no initial disturbance more than that seen after isotonic sodium chloride injections.

Blood.—Heparinized blood, 0.01 cc., was injected suprachoroidally in four pigmented rabbit eyes and four albino eyes. Twenty-four hours following injection there was no reaction in the pigmented eyes. The albino eyes showed some engorgement of the choroidal vessels in the vicinity of the injection, and a definite blush of the free blood could be seen. The area was poorly demarcated. After one week all eyes showed normal fundi.

Melanin Pigment.—The choroidal tissues of several pigmented rabbit eyes were ground in a mortar and pestle and mixed with 2 cc. of isotonic sodium chloride solution. A brownish-black solution resulted, with small clumps of pigmented tissue in suspension. Both eyes of an albino rabbit were injected with 0.01 cc. of the suspension. Immediately after the injection the brownish-black pigment could be seen lying deep in the fundus; the melanin pigment lay in an area of about 1.5 D. D. at the usual site. Observation over a period of one and one-half months showed gradual and complete disappearance of the pigment.

SUBRETINAL INJECTION

As close contact as possible with the retinal elements is desirable in the study and treatment of the effects on the retina of various substances, such as blood, antigens, carcinogens, metals, toxins, and bacteria. Entrance to the subretinal space through the choroid is barred because of the delicacy and vascularity of the latter. The optic foramen through the sclera is relatively avascular, and the choroid has been shown to ring it neatly in the rabbit.[16] This point makes the easiest approach to the subretinal space. The animal is prepared as in the suprachoroidal injections, and the procedure is the same except that the point of the needle engages the optic nerve, is slid in its sheath through the scleral canal, and follows the bend of the nerve fibers, thus entering the subretinal space. The manipulation is more difficult than the suprachoroidal procedure, as the retina is prone to tear at the emergence of the nerve fibers from the scleral canal. An orienting subretinal injection of India ink was done and is shown between the retina and the choroid (Fig. 9). The retina, with the bleb of ink, was detached in fixing and sectioning. The ophthalmoscopic picture of a subretinal area of India ink shows a bleb of about 1 D. D. lying below the nerve head, well demarcated, and with normal surrounding fundus. The edges are finely feathered, probably because of the separation of the cells in the rod and cone layer (Fig. 9). Immediately after flattening of the bleb the particles presented a stippled random distribution, within a roughly circular area. This picture has not

changed after two months, and this lack of movement is in sharp contrast to the migration of the particles seen following suprachoroidal injection of India ink. That the passage of the various fluids used did not meet the resistance encountered in the suprachoroidal technique was probably due to the absence of fibers between the retina and the choroid.

Subretinal Carcinogenic Agents.—Cholesterol was used as a matrix in forming granules of 3-methylcholanthrene.[17] Particles small enough to fit into the bore of a No. 21 needle were selected for implantation into the subretinal space. The No. 21 needle with a stylet in place is inserted as in the usual procedure, and after the

Fig. 9.—Subretinal bleb of India ink. The retina was detached by the knife. Particles lie between elements of the rod and cone layer.

needle point is positioned, the granule of carcinogen can be left in the subretinal space by withdrawing the needle back over the stylet. If, on the other hand, the granule is pushed out of the needle, there is a greater tendency to tear the retina with the sharp edges of the granule. This procedure was carried out in three rabbit eyes. The yellowish mass of material can be clearly seen under the retina, compressing the choroidal vessels in the immediate vicinity. There have been no reactions, inflammatory or neoplastic, to the carcinogen for a period of four months. Studies are to be carried out using other carcinogens.

Blood.—An injection of 0.005 cc. of blood can be readily made between the retina and the choroid. Successful injections were done in three eyes of pigmented

rabbits. Following the injection, the deposit assumes a cyst-like, rounded shape; the margins are minutely feathered, as in the India ink injections, and there is definite elevation of the retina. The deposit is well demarcated, and the adjoining retina is clear. The blood does not have any tendency to migrate. After 24 hours fluid levels can frequently be seen, with a grayish-white superior level and a dark-red lower area, probably a settling out of the red blood cells. The entire surface gradually becomes whitened, and after three to four days many small vitreous opacities appear over it and extend well out toward the lens. The vitreous reaction gradually increases until there is a marked clouding of detail in the involved retinal area. After three to four weeks there is gradual clearing of the vitreous, and the blood is seen to be completely absorbed. Minor pigmentary disturbance is present, and a few white exudates remain on the retina after one month.

Horse Serum.—1. Unsensitized Rabbit: Horse serum, 0.005 cc., was injected subretinally in two eyes. Twenty-four hours following injection the retinal bleb had incompletely absorbed and there was a faint vitreal haze overlying. This became denser, forming a heavy, semilinear, veil-like opacity close to the retina. The adjoining fundal markings were normal. After a week there was almost complete absorption of the vitreous opacity.

2. Sensitized Rabbit: Subretinal injections of horse serum (0.0025 and 0.0075 cc.) were done in four eyes of rabbits previously sensitized. The reactions in general were as follows: Within 24 hours there was a marked chorioretinal reaction, with whitening in the area of the subretinal bleb and overlying vitreal haziness. In several eyes small subretinal or choroidal hemorrhages lay adjacent to the involved area. These gradually spread from the involved site and were accompanied by spread of the vitreous haze.

The anterior chamber remained clear in eyes (two) receiving 0.0025 cc. of horse serum subretinally. A marked anterior chamber reaction of beam, flare, and precipitates appeared in eyes four days after injection of 0.0075 cc. subretinally. The severity of the fundal and anterior chamber reactions coincided roughly, gradually dying out and becoming quiescent in two to three weeks.

3. Locally Sensitized Rabbit: One cubic centimeter of horse serum was given intravenously two weeks after the subretinal injections of horse serum had been done. A marked chorioretinal and vitreal reaction ensued, similar in appearance and extent to that observed in the generally sensitized rabbit.

CONCLUSIONS

I. *Suprachoroidal Injection.*—A method of injecting various substances, including viable cancer tissue, bacteria, dyes, beryllium, pigmented choroidal tissue, alloxan, and horse serum, into the suprachoroidal space is presented. The results were as follows:

1. India ink, 0.02 cc., injected into the suprachoroidal space gives a black reflex to the albino rabbit eye.

2. India ink particles injected in the suprachoroidal space tend to migrate to the choroidal vessel wall.

3. Pure metallic beryllium lying in the suprachoroidal space for five months does not cause an apparent inflammatory reaction.

4. Injection of 0.005 cc. of a suspension of bovine tubercle bacilli, 200 per high-power field, in the suprachoroidal space causes a marked, rapid chorioretinitis, which is confined to choroid and retina for the first two or three weeks following injection.

5. Squamous-cell carcinoma, V-2 of the rabbit, grows in its characteristic fashion in the choroid of the rabbit eye.

6. The injection of 0.01 of a dye, *Lichtgrün*, into the suprachoroidal space is absorbed in four days.

7. Injection of 0.005 cc. of staphylococci, 1,000 per cubic centimeter, into the suprachoroidal space causes transient hyperemia of the choroidal vessels, with some disturbance of the vessel wall.

8. Suprachoroidal injection of 0.01 cc. of horse serum into the sensitized rabbit causes transient engorgement of the choroidal vessels and mild pigmentary disturbance at the site of the injection.

9. Injection of 0.01 cc. of 0.3 M alloxan into the suprachoroidal space does not cause more vascular disturbance than that seen following injection of isotonic sodium chloride solution.

10. Choroidal pigment from colored rabbits, in the concentration used injected into the suprachoroidal space of albino rabbits, is absorbed in four to six weeks.

11. Injection of 0.01 cc. of rabbit blood into the suprachoroidal space is completely absorbed in 48 to 72 hours, without residual reaction.

A special syringe, necessary for subchoroidal and subretinal injections, which will accurately repeatedly deliver from 0.0025 to 0.05 cc. by an automatic setting device, is described.

An improved rabbit box for the performance of this operation under local anesthesia is shown.

II. *Subretinal Injection.*—A method of injecting and planting various substances into the subretinal space is described. The following observations were made:

1. Injection into the subretinal space does not meet the resistance encountered in suprachoroidal injections, and fluids assume a bleb-like form.

2. Subretinal injection of 0.005 cc. of blood (autogenous) causes a marked reaction in the overlying vitreous, with formation of opacities extending toward the lens.

3. Pigmentary disturbance and exudate remain after subretinal blood is absorbed.

4. A carcinogen, 3-methylcholanthrene, in cholesterol does not cause inflammatory or neoplastic changes in the retina when implanted subretinally.

5. Subretinal India ink does not migrate after the saline vehicle is absorbed.

6. There is mild vitreal reaction to subretinal horse serum in the unsensitized rabbit.

7. There is marked retinal, choroidal, and vitreal reaction to subretinal horse serum in the sensitized rabbit. In rabbits receiving 0.0075 cc. subretinally a marked anterior chamber reaction occurs, coinciding roughly with the posterior lesion in severity and duration. Rabbits receiving 0.0025 cc. show clear anterior chambers.

Suburban Square Building.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

FIBROTIC HYPERTROPHY OF THE PLICA SEMILUNARIS

THE CASE of fibrotic hypertrophy of the plica semilunaris to be reported is interesting because in a review of the available literature it was found that a similar condition has not previously been reported. The appearance of the plica semilunaris when the patient was first seen suggested the presence of a new growth,

Fig. 1.—Appearance of the plica semilunaris in the right eye.

possibly malignant. Its benign nature has later been confirmed, but the etiological factor responsible for the condition has not been determined despite close study of the case and several consultations with ophthalmologists, both local and from the United States.

Mrs. E. M. G., a married 29-year-old white woman, came to see me in December, 1951, complaining of a fleshy growth in the right eye of one year's duration which was still growing. She had itching and slight discharge in both eyes, worse in the right one.

The external examination of the right eye showed a hard, hypertrophied, and congested plica semilunaris (Fig. 1). Even with the eye closed it could be felt through the upper eyelid. A small pterygium was present in nasal side of the right eye, invading the cornea for 1 mm. Both eyes showed a slight congestion of the palpebral conjunctiva; the rest of the bulbar conjunctiva was normal. The plica semilunaris of the left eye was slightly reddened, but it was not hard.

From the Section of Ophthalmology, School of Medicine, University of Puerto Rico.

The examination of the eyegrounds was negative.

Vision was 20/20 in each eye without correction.

A tentative diagnosis was made of mild chronic conjunctivitis in both eyes and a possible new growth of the plica semilunaris of the right eye.

A Wright-stained smear of the conjunctival secretions showed only a few epithelial cells and leucocytes; there were no eosinophiles. A Gram-stained smear was negative. Cultures of the conjunctival secretions in blood agar and thioglycollate broth were negative.

General physical examination was negative. A complete blood examination showed RBC 4,800,000, Hgb 82%, WBC 10,600, and a differental count of neutrophiles 42%, lymphocytes 4%, eosinophiles 8%, and monocytes 1%. The blood Kahn test and urinalysis were negative. Consultation with an otolaryngologist revealed only a mild catarrhal ethmoiditis.

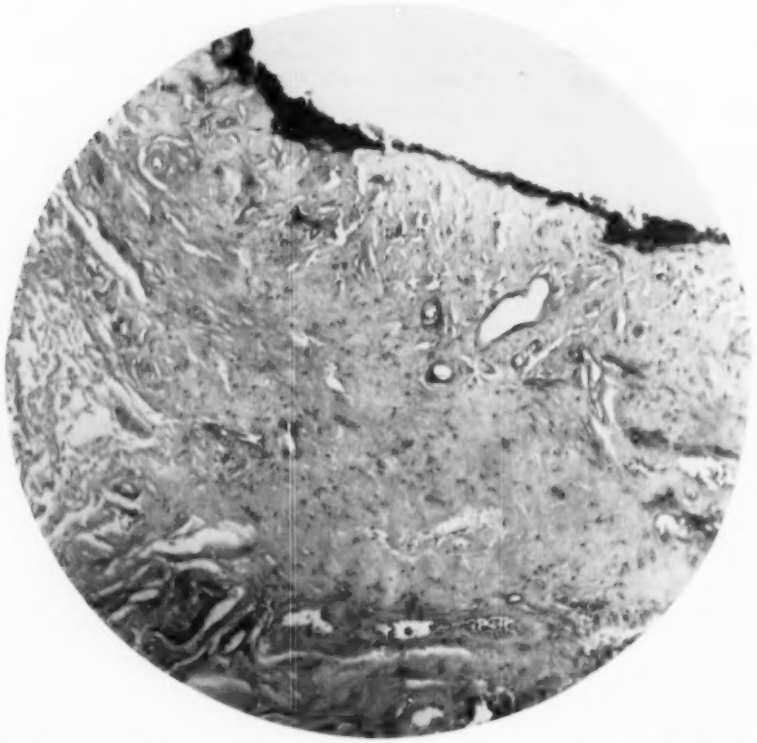

Fig. 2.—The central part is edematous, while the peripheral portions are composed of dense fibrous tissue. The conjunctiva shows alternating areas of atrophy and slight hyperplasia. × 80.

Local treatment to the right eye with chloramphenicol (Chloromycetin) eye drops every two hours, chloramphenicol ointment at bedtime, multivitamins, and antihistaminics by mouth was given for two weeks, without improvement. Then it was decided to use cortisone eye drops, 0.5% solution, every hour, but the condition remained unchanged.

A month after the patient was first seen, a biopsy specimen was taken from the upper horn of the plica semilunaris of the right eye.

Pathological Report.—"Gross Study: The specimen is composed of a small portion of tissue measuring 0.3 cm. in the main diameter and 0.1 cm. in thickness. Externally it is light-gray and finely fibrillary. All the specimen was embedded.

"Microscopic Study: Most of the sample is composed of fibrous tissue that is moderately well vascularized (Fig. 2). The fibrous tissue becomes dense and collagenous in the peripheral parts, but in most of the central portions it is of edematous appearance. This edematous appearance extends to the walls of the small blood vessels. One side is covered by conjunctiva that in places is slightly broadened and in others is atrophic. A Van Gieson stain shows well the collagen fibers at the periphery, while the central parts (Fig. 3) stain green and contain relatively few red fibrils. Despite the color reaction, the green areas probably represent simple edema and not an amyloid infiltration. Special stains for amyloid could not be applied because the biopsy specimen was so small that it was embedded in paraffin in its entirety.

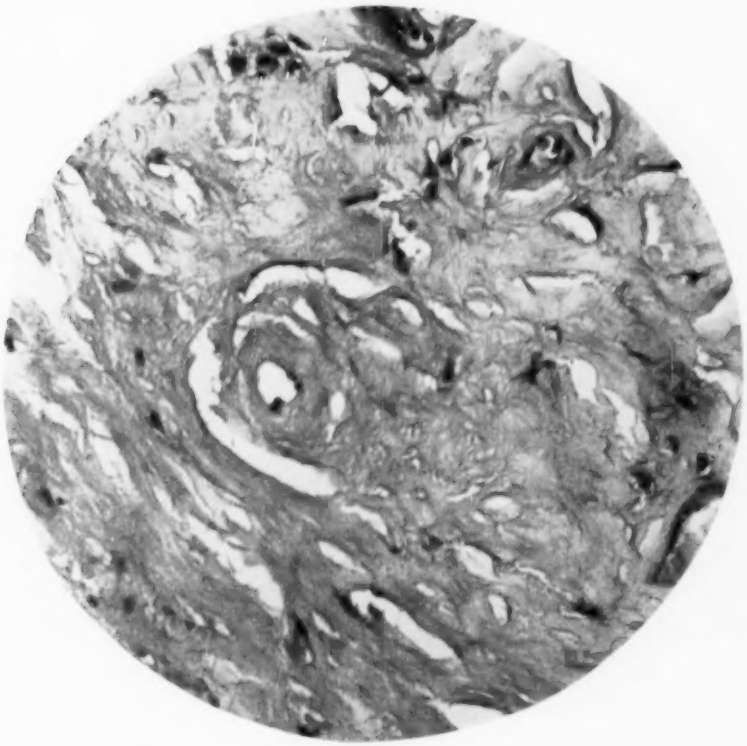

Fig. 3.—Van Gieson stain, showing the edematous central parts with relatively few fibroblasts. × 360.

"Diagnosis: Fibrosis and edema of the plica semilunaris, of undetermined cause."

Further Course.—About two months afterward some hardening and hypertrophic changes were first noticed in the plica semilunaris of the left eye, but these were much less marked than in the right eye. The right eye was then unchanged. During the past year the appearance of both semilunar plicas and the subjective symptoms of slight discharge and itching have remained unchanged in spite of the use of other antibiotics, such as propionate compound (Propion), nitrofurazone (Furacin), and oxytetracycline (Terramycin) eye drops.

Lately it has been noticed that, aside from the findings in both semilunar plicas, there is now some thickening and congestion of the bulbar conjunctiva under the upper eyelid, running from the upper fornix downward for about 8 or 10 mm. and appearing as a prolongation of the upper horn of the plica semilunaris upward and temporally to near the external canthus. In the left

eye is found a similar hypertrophy of the bulbar conjunctiva, but less pronounced than in the right eye. This thickened bulbar conjunctiva sometimes forms a fold beneath the upper lid which simulates another plica semilunaris.

SUMMARY

The case is reported of a young woman of 30 who presented a raised induration of the right semilunar fold. Biopsy proved this to be due to fibrosis and edema. The plica of the opposite eye has shown a clinically similar involvement, but to a much less degree. Although there is no way of proving it, we are inclined to explain the change in the semilunar fold as an extremely rare sequel of a mild chronic conjunctivitis. Perhaps this induces a proliferation of fibrous tissue in the plica, with a local circulatory embarrassment that manifests itself as edema.

Dr. Enrique Koppisch, Professor of Pathology, University of Puerto Rico School of Medicine, made a study of the pathological material in this case.

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BENIGN CALCIFYING EPITHELIOMA

BENIGN calcifying epithelioma is a lesion which is not uncommon among the tumors of the head and neck. Inasmuch as it is rarely diagnosed preoperatively when occurring in the ocular region, this case report is intended to direct the ophthalmologist's attention to this tumor in the differential diagnosis of neoplastic lesions of the lids and orbital area.

The tumor, occurring usually in young adults, and predominantly in females, is generally small (1 to 3 cm.), but sizes up to 9 cm. have been reported. It is well circumscribed, of a hard consistency, and freely movable beneath the skin but adherent to it. Histologically, the mass is encapsulated, and, according to Côté, is characterized by "necrotic masses of squamous epithelium, variable amount of viable basal cell type epithelium, calcification, and invasion of the necrotic mass by active fibroblastic tissue in which foreign body giant cells appear in profusion . . . differentiating it at a glance from the ordinary sebaceous or epidermoid cyst with which it may be confused clinically."

REPORT OF A CASE

Mrs. G. G., white, aged 29, was a patient of Dr. John G. Di Francesco, Brooklyn. On routine examination, a pea-sized mass was noted beneath the skin over the right supraorbital notch. The patient stated that the mass had been present 20 years, had remained unchanged, and was not tender. It was diagnosed clinically as sebaceous cyst. Six months later the patient returned with pronounced pain and tenderness in the region of the mass. The pain radiated to the bone. Sinus studies were done, with negative findings. The pain persisted and was relieved only by 2% procaine injections. The diagnosis was then "neurinoma." After consultation it was decided to excise the growth. This was done with use of local anesthesia. The mass was found to be attached to overlying skin but was excised *in toto*. The patient made an uneventful recovery.

Pathological Examination.—Gross examination revealed a whitish, rounded, hard mass, measuring 2 by 2 cm. The fibrous capsule was intact. Microscopic study showed sheets of necrotic keratinized epithelium, with intermingled stroma of loose fibrous tissue. Numerous calcified plaques were seen throughout the mass.

Diagnosis.—The diagnosis was benign calcifying epithelioma of the skin.

Miss Jean Gareri prepared the microscopic sections and Mr. John Goeller the photomicrographs.

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From the Eno Laboratory, New York Eye and Ear Infirmary.

Fig. 1.—Low magnification, showing (*A*) necrotic squamous epithelium, (*B*) loose fibrous tissue stroma, and (*C*) calcified epithelial plaque.

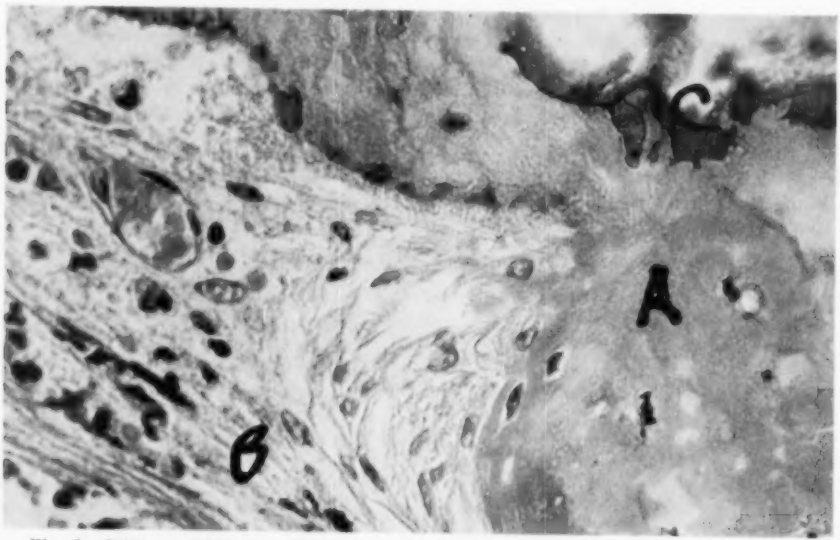

Fig. 2.—High magnification, showing (*A*) necrotic keratinized epithelium, (*B*) fibrous tissue stroma, and (*C*) calcification.

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Annual Reviews

LENS AND VITREOUS

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SINCE the last review of this subject [1] a number of papers have been added to the literature of the lens and vitreous. Further work has been done on the chemistry of the lens and on the physical structure of the vitreous. Work on irradiation cataract and on lens changes associated with altered carbohydrate metabolism has been continued. In addition to these papers which are slowly advancing our knowledge of the mechanism of cataract formation, many discussions of the practical surgical management of cataract have appeared.

THE LENS

"A Medical Fish Story."—Unfortunately, the publication in *Science*,[2] by an author who is not a physician in collaboration with two physicians who are not ophthalmologists, of a "nonsurgical treatment of cataract" received wide notice in the lay press. The alleged beneficial effects on cataracts of parenteral injections of a preparation of fish lens protein caused such widespread public interest and hope that the Committee on Ophthalmology of the Division of Medical Sciences of the National Research Council [3] felt obliged to issue a report on the subject. This report reviews the entire literature on lens protein in the treatment of cataract and points up the lack of evidence of its efficacy. It further criticizes the experimental work said to be the background of this new "cure" by pointing out that galactose cataracts in rats will improve spontaneously when galactose administration is stopped. It is suggested that fish lens protein treatment was given at the point where the cataracts would have cleared spontaneously without treatment. A subcommittee of ophthalmologists had examined some of the human cases and were unable to substantiate the claims of improvement. Furthermore, it is reported that of 12 sample bottles of material for injection treatment, 10 were contaminated with pathogenic organisms. The committee report concludes:

> Because of the total lack of evidence that the lens antigen treatment of cataract described by Mr. Shropshire . . . has any efficacy; because adequate evidence is now available to the Committee that it is, in fact, without demonstrable efficacy; and because treatments of this type have been thoroughly investigated in the past and proved not only invalid but potentially dangerous to the patient; this Committee does not recommend further investigation of this treatment by any agency.

Nevertheless, many patients with various types of cataracts have been subjected to fish lens protein injections. Posner * and Breinin [6] point out the danger of this treatment. Posner [4] cites a case of uveitis, presumably from seepage of lens matter through the capsule, in a patient sensitized by fish lens protein injections. This patient was helped by intracapsular extraction of the lens. He warns of the danger of severe phacoanaphylactic endophthalmitis. Breinin [6] cites three cases following this treatment—one with uveitis and glaucoma, responding only to bilateral intra-

* References 4 and 5.

capsular operation; one with uveitis before operation; one with uveitis and a stormy course after extracapsular extraction. He suggests that corticotropin and cortisone are useful in the management of these cases. He also urges intracapsular operation and cutaneous testing for lens sensitivity in patients who have had such injections.

Although most of the problems caused by lens protein injections were concentrated in the United States, sufficient publicity filtered across the Atlantic to cause the *British Journal of Ophthalmology* to reprint an editorial from *The Journal of the American Medical Association* entitled, "A Medical Fish Story."[7]

Apparently, nonsurgical treatments for cataract continue to crop up. Schmidt[8] felt compelled to evaluate a mixture of lens protein, riboflavin, ascorbic acid, potassium iodide, and strychnine. He found this combination a failure in 20 cases in which it was tested. A few patients thought they saw better, but Schmidt attributes this effect to the action of strychnine on the retina. Apparently he did not consider the possible psychic effect of suggestion. Davids[9] advises, for nonoperative treatment of senile cataract, general medical and geriatric therapy. He also suggests a vitamin-rich diet, supplementary vitamins, and hormones, including testicular extract and estrogen. Proof of any directly beneficial effect on cataracts seems lacking.

The Ridley Lens.—Wide interest has been shown in Ridley's ingenious and dramatic operation for replacing a cataract by an intraocular acrylic lens. His first report in this country[10] brings his total number of cases up to 63. He reiterates the well-known handicaps of ordinary aphakic vision and the difficulties of monocular aphakia. The use of contact lenses to overcome some of these difficulties is dismissed without much consideration. He then describes his technique for performing an extracapsular extraction with a round pupil and inserting the acrylic lens between the iris and the posterior capsule. Specifications of the artificial lens are given in detail. He appears very satisfied that over 50% of his patients attained a final corrected visual acuity of 6/9 (20/30) or better, and half of these 6/6 (20/20).

Complications are described in detail. All cases have prolonged postoperative reaction with considerable fibrin and pigment migration. The reaction clears with cortisone in "several weeks" to "considerable time." In two cases after extracapsular extraction the acrylic lens became subluxated. In two after intracapsular extraction it became totally dislocated into the vitreous. In four cases he was unable to insert the lens, for various reasons, and in an 84-year-old patient the lens was extruded. One case developed iris incarceration and glaucoma, while two others developed glaucoma which could be controlled with miotics. One iris prolapse was replaced, and one eye with cloudy posterior capsule was needled from behind.

Ridley considers that in 90% of the cases the course was essentially uneventful except for the prolonged plastic iritis. The lenses were generally well tolerated and remained clear.

In his discussion of this presentation, Vail † emphasizes caution and conservatism, stressing the need for time in the evaluation of a new and essentially experimental procedure. Similarly, deRoetth,[11] while agreeing with the optical advantages of an intraocular lens, urges caution, citing the dangers of postoperative iritis and possible late dislocation and late foreign body reaction. He further compares his

† Vail, D., in discussion on Ridley.[10]

own visual results in 406 successive cataract extractions with Ridley's visual results. DeRoetth obtained visual acuity of better than 20/30 in 87.2% and found consistently similar results in the literature, where all modern reports approach or better 90%. Ridley's 50% compares very poorly with such results. Arruga,[12] too, sounds a note of caution, stressing the importance of long-term follow-up studies. He feels that the operation is indicated in completely opaque monocular cataracts but contraindicated in the presence of increased pressure or evidence of old iritis or cyclitis. It may be done in cases of traumatic cataracts if the posterior capsule is intact and in cases of heterochromia if there is no inflammatory reaction. He reports five cases of monocular cataract in which he has performed the Ridley operation. In one vision of 7/10 and fusion were obtained. In another acuity was 4/10 and the eye diverged. In a third an implant was inserted after intracapsular extraction. This patient had an acuity of 8/10 until the lens became dislocated into the vitreous, when the vision improved to 1.0. In a fourth case glaucoma, which had readily been controlled by miotics before operation, got out of hand and required retrociliary diathermy. Details of his fifth case are not given. Arruga has devised his own forceps for handling the acrylic lens and for settling the iris over it. He finds the iris fixed to the acrylic in the early postoperative period, regaining some mobility later. The principal problems still to be evaluated are the long postoperative inflammation and the failure of the visual acuity to match that with standard operations, particularly the intracapsular ones. Patel[13] has made a slight modification, introducing a lacrimal needle to move the iris over the implant with a stream of saline. Miller[14] devised a suction cup to hold the lens as it is inserted and injected 0.2 cc. of cortisone acetate, 25 mg. per cubic centimeter, directly into the anterior chamber, followed by introduction of an air bubble. He reports 10 cases which make him feel that the operation is worth while in monocular cataracts. Others‡ report personal experiences, and Malbrán and Salleras[16] think that the operation may be perfected, so that it may have a great future. They suggest that the presence of the acrylic lens prevents anterior displacement of the vitreous, which, in turn, might reduce the incidence of retinal detachment and corneal edema.

OTHER SURGICAL FACTORS

Anesthesia.—Further reports indicate an increased interest in curariform agents for general akinesia in cataract surgery. Barraquer Moner[17] presents another 500 cases, bringing his total to 1,500 cataract operations under curare. He now finds the most satisfactory technique to be continuous intravenous injection at the rate of 1 mg. per minute until the desired effect is attained. The onset of ptosis is an indication of sufficient drug. The total dose varies from 3 to 25 mg. The effect lasts 15 minutes after injection is stopped. He has had trouble with anoxia in 3% of his patients and uses oxygen as a supplement, given at the rate of 12 liters a minute. This method has proved very satisfactory in his hands, for, whereas he was losing vitreous in 4 to 6% of cases under local akinesia, he has been able to run a series of 100 successive cases without vitreous loss under curare. Further evidence of the safety of the method is given by the increased dilatation of the pupil when aqueous escapes. This is due not to a direct curare effect on the iris but to a sinking back of the lens from hypotony. Henderson[18]

‡ References 15 and 16.

also finds that tubocurarine reduces the incidence of vitreous loss. He considers abolition of ability to look up the proper index of sufficient dosage. He prefers an initial dose of 3 mg., followed by continuous administration at a rate not faster than 1.5 mg. per minute. This is the technique which the previous author has abandoned. Of 138 successive cases, Henderson had difficulty with 12. Five patients had the drug poorly administered; two were hypersensitive; two had respiratory difficulties, and three did not attain satisfactory relaxation. Agarwal [19] finds dimethyl tubocurarine iodide superior to tubocurarine or gallamine triethiodide. This drug produces the same fall in intraocular pressure and the same muscular relaxation with a smaller and safer dose. Girgis [20] reports that mephenesin (Myanesin) produces a similar and safer relaxation when given by mouth as an elixir.

Atkinson [21] studied the preferences of ophthalmic surgeons by mailing a questionnaire concerned with local anesthetics. He concludes that the choice sedative is a combination of meperidine, pentobarbital, and an antihistaminic. He urges careful psychologic preparation of the patient, test doses of drugs to be used, mild sedation for 24 hours before operation, and careful timing of the sedative for maximum effect. Schillinger [22] refers the more accurate timing of pentobarbital sodium by continuous intravenous drip during operation. He [23] also suggests that better topical anesthesia over the site of a superior rectus suture is obtained by introducing an irrigating stream of the anesthetic up under the lid with a blunt needle.

Instruments.—A number of minor improvements in instruments have been recorded. Castroviejo [24] describes a set of two pairs of curved scissors for enlarging incisions, stressing the importance of having the interior blade posterior on each side. He [25] also reports a new suction pump the electric motor of which can also drive a dacryocystorhinostomy drill. McCoy [26] advises light vinyl tubing and a nylon needle adapter to increase the ease of manipulation of suction equipment. Nugent [27] suggests a small suction cup to hold the Ridley lens and a double-barreled needle for combined aspiration and irrigation. Hartman [28] also favors a "two-way syringe" for soft cataracts. Atkinson [29] has modified a cystotome to help in inserting preplaced sutures and making ab externo incisions.

Techniques.—As the perennial debate on knife *vs.* keratome-scissors section continues, Hildreth [30] points out, in a historical review, that Daviel in 1752 described a keratome-scissors incision not too unlike the one favored by many today. Randolph and Eareckson [31] studied carefully 150 knife sections and 150 keratome sections in otherwise similarly performed lens extractions. They report no statistically significant difference in operative complications, postoperative course, or final visual acuity.

Goar [32] reviews his rich experience in 32 years of cataract surgery and outlines the methods which this experience has brought him to recommend today. These consist of local anesthesia, Van Lint akinesia, retrobulbar block with epinephrine and hyaluronidase, lid sutures, and superior rectus suture. Section is made with keratome and scissors, and a sliding flap and three postplaced radial appositional sutures of 000000 chromic absorbable surgical (gut) suture material are used. The cataract is extracted in capsule by forceps or suction cup. The round pupil method is preferred, although it is suggested that the combined operation may be safer. Air is instilled in the anterior chamber unless the hyaloid is

broken. (It is interesting to note that various other surgeons consider that air is indicated only when the hyaloid is broken.) A monocular dressing is used and the patient allowed up on the first or second postoperative day. The only complication discussed is epithelial downgrowth, which Goar feels must be commoner than reported statistics indicate. He advises early x-ray treatment for this condition. Extraction of monocular cataract is recommended to avoid the glaucoma associated with hypermaturity. When such a reaction occurs, intracapsular operation is urged. This author has had fair success with contact lenses in unilateral aphakia. His experience is to be contrasted with Ridley's dismissal of contact lenses.[10] Goar uses extracapsular extraction in young people and finds ultraviolet light an aid in irrigating the cortex. Through-and-through discission is preferred for congenital cataracts, for linear extraction is considered too dangerous.

Sobanski [33] reports a "new method" for extraction of hard cataract which consists essentially of use of a new forceps for sliding delivery. He broke 33 capsules in 116 cases—12 before extraction and 21 during delivery. Salleras [34] advocates broad iridectomy above, radial iridotomy below, and postoperative use of atropine and cortisone for cataracts complicated by chronic iridocyclitis and glaucoma. In another report [35] he describes lens extraction at the time of penetrating keratoplasty. Eleven cases were said to be improved, but none achieved acuity up to 0.1. Birge [36] again reports on single-pillar iris inclusion at the time of cataract extraction as a combined operation when glaucoma and cataract coexist.

Complications.—Post and Harper [37] found glaucoma after cataract extraction in 35 eyes of 30 patients out of 500 consecutive cases in which glaucoma had not been present preoperatively. They studied this series statistically and found that in all but four eyes there had been operative complications. Vitreous loss was commonest (12 eyes), with hyphema (5), iritis (5), flat chamber, choroidal detachment, retinal detachment, and vitreous in the wound after operation (2 each), and iris prolapse, epithelial downgrowth, corneal edema, wound infection, and severe vomiting (1 each) following. They suggest that postoperative glaucoma can usually be managed successfully if the surgeon is alert and looks for it after all complications. Ross [38] reviewed the same subject and collected 22 cases from the literature. He found that flat anterior chamber and iridocyclitis were the most important factors, although most cases also had other complications.

On the other hand, Christensen and McLean [39] discuss cataract as a complication of glaucoma operations. They found 17 cases of lens injury in 47 eyes which came to enucleation after glaucoma surgery. Lens capsules were perforated, and the lens and iris were apt to be in granulation tissue at the operative site. Uveitis varied from mild infiltration to an acute reaction, like phacoanaphylaxis. They recommend more care in glaucoma surgery and lens removal for subsequent uveitis, which may be due to unrecognized lens damage.

Phacoanaphylaxis was studied by Law,[40] who reviewed six cases. Five had had extracapsular extractions on both eyes with reaction after the second operation. He raises the question of the relation of this condition to sympathetic ophthalmia and reviews the theories of sensitivity to lens protein and toxicity. Scheffler [41] reports a case in a 61-year-old diabetic woman who developed bilateral granulomatous uveitis two months after a cataract extraction with much retained cortex. Clinical diagnosis of sympathetic disease was made. Eventually the "sympathizing"

eye was enucleated for intractable glaucoma after the eye operated on had become quiet. Histological study showed the picture of phacoanaphylaxis, but the condition did not appear to be sympathetic uveitis. The nature of the granulomatous iritis was not fully explained.

DeVeer [42] also reports the histological appearance of a "second eye" in endophthalmitis phacoanapylactica. His patient was a 65-year-old man who first had an iridencleisis for chronic primary glaucoma. This was followed by a cataract in the same eye six months later, which was extracted extracapsularly 30 months after glaucoma surgery. Severe postoperative reaction and delayed absorption of cortex were followed in seven weeks by hypopyon. Four months later this eye was shrunken and sightless. The fellow eye, not operated on, became acutely painful after an automobile accident, nearly six months after the cataract operation. The shrunken, aphakic eye did not flare up. A clinical diagnosis of sympathetic ophthalmia was made. Seven months later, after intensive treatment, including cortisone and antibiotics, this "sympathizing" eye was removed. Sections showed a rupture of the anterior lens capsule with the typical cytological reaction of phacoanaphylaxis around the lens matter. Histologically the condition was distinct from sympathetic ophthalmia.

These several reports reflect a revival of interest in the problem of lens sensitivity and the clinical similarity of bilateral lens-induced uveitis to sympathetic ophthalmia. Scott [43] reports three cases of traumatic rupture of the lens capsule followed by milky fluid in the anterior chamber and acute glaucoma. He attributes the reaction to the toxicity of lens protein and mechanical blockage of the filtration angle. In all eyes improvement followed irrigation.

Hemorrhage in and after cataract operations was studied by Heinz,[44] who found venesection before operation ineffective, and by Giardini and Nizetic,[45] who conclude that mechanical strain on the wound, rather than capillary fragility, is responsible for postoperative hyphema.

Cinotti and Jacobsen [46] analyzed 1,001 cataract operations for complications of various sorts. They found that diabetics were more prone to secondary glaucoma, hemorrhage, and iritis, regardless of the blood sugar level at the time of operation. The usual preoperative tests for macular function proved disappointingly inaccurate. They were unable to show significant differences in the incidence of complications when comparing silk sutures with surgical gut sutures, knife sections with keratome sections, or round pupil extractions with iridectomies. In at least 60% of cases postoperative hyphema was caused by trauma. They felt that iridocyclitis was the most serious complication. Their five cases of epithelial downgrowth were treated with radiation, but the final outcome is not stated.

Smith [47] recommends deliberate vertical sphincterotomy of the iris below for vitreous loss and in linear extraction of congenital cataracts, citing six illustrative cases.

Infection.—Callahan [48] studied infection in 1,653 cataract extractions and found an incidence of 0.3% (5 cases). All five eyes were lost and three of them enucleated. He notes the increasing importance of Gram-negative organisms in these days of antibiotics. An enthusiast for preoperative cultures, he decries the increasing tendency away from this practice. In 260 of his cases operation had been postponed because of positive cultures. He feels that many eyes were saved by this step. It

is interesting to note that his incidence of lost eyes from infection is not materially lower than the general average and that if many of his 260 cases of postponed operation had otherwise been lost his rate might have been alarmingly high.

Rauh [49] advocates use of sulfonamide powder in the upper cul-de-sac at the end of operation and of penicillin-sulfathiazole ointment at each dressing. He had 215 successive cases without infection, lost 2 from contaminated miotic solutions, and then had 102 cases without infection.

Wound Healing.—Fry [50] describes the pathological picture in a eye of an elderly diabetic that would not heal. She had previously had an uneventful cataract extraction in the other eye. The operation was uncomplicated, and wound closure with absorbable surgical sutures U. S. P. was adequate. Repeated iris prolapses were repaired with nonabsorbable (silk) sutures, but healing never took place and eventually on the 52d day enucleation was performed. Sections showed a gaping wound containing a few epithelial cells and very few fibroblasts. Subchoroidal hemorrhage was present, but there was no iris infiltration and exudate was minimal. Without fault in technique or trauma, the failure to heal is unexplained. No mention is made of the use of adrenal steroids.

Kara [51] had the unusual opportunity of sectioning an eye which had had an uneventful cataract extraction four days before. Accurately placed chromic absorbable surgical sutures U. S. P. are seen in section, with some necrosis about the suture material. In spite of tight suture closure, there is gaping of the posterior lips of the wound. This paper is excellent confirmation in a human eye of some of the experimental animal work of Dunnington and Regan, cited in last year's review.[1]

EXPERIMENTAL STUDY

Research on the structure of the lens, particularly experimental lens opacities, continues to attract great interest, as indicated by the number of papers published in the past year.

Structure.—Monahan,[52] using phase-contrast microscopy, studied a large number of lens capsules, both normal and cataractous, from human and animal eyes. He found minute linear streaks, which he interprets as minute channels. They are absent at the anterior pole and in the posterior capsule. In the rest of the anterior capsule they run radially, entering the anterior surface at an angle of 15 to 20 degrees and coursing toward the equator. More peripherally they may branch and enter the potential space between epithelial cells. They are not found in very young human eyes or in any animal eyes, including those of monkeys. The number decreases in aged lenses and in immature cataracts. Monahan feels that these hitherto undescribed channels are not artifacts and their diminution in old age, by reducing metabolic exchange, may account for senile cataract.

In another study by phase microscopy, Asayama and Nakashima [53] compared normal and cataractous human lenses. In normal capsules they found stellate cells, which in cataractous lenses had perinuclear vesicles. The globule of Morgagni as seen with the ordinary microscope has a sharp phase contrast, suggesting that it has a marked chemical difference from surrounding tissue.

Undoubtedly, future studies with this new microscopic technique will serve to elucidate further the new anatomical features now attracting investigators.

Dorello,[54] examining 50 cataractous lenses histologically, noted collections of small fat-like spherules. He found no relation between type of cataract and distribution of the material.

Hart and Peckham[55] studied the specific gravity of rat lenses, using a gravity column. By plotting specific gravity against age, they obtained a curve which can be closely superimposed on Duane's chart of amplitude of accommodation in human eyes. It is suggested that the variations in both are related to the change with age in the plasticity of the lens.

Carbohydrate Cataracts.—Studies of the lens changes caused by sugars continue both in the experimental animal and in clinical observations. Clinically, Huggert[56] stresses the change in the band of disjunction as an early sign of juvenile diabetes. Patz[57] reports three cases of cataract in children with galactosemia and discusses 27 other cases culled from the literature. His case showed the typical central refractile ring, resembling the "oil-drop" effect of lenticonus. They had the typical zonular cataract, vacuoles, and punctate opacities on the surface of the fetal nucleus. Removal of the sources of galactose from the diet of these children resulted in regression of the cataracts, in one case to normally clear lenses. Steiner[58] reported another case of improvement on milk-free diet. This child had the usual malnutrition, hepatomegaly, galactosemia, and galactosuria seen with galactosemia and lamellar cataracts.

Patterson[59] showed in diabetic rats that insulin prevents cataract formation and restores the normal growth curve. Lowering the blood sugar by phlorhizin also prevents or delays cataract formation. He also showed that glucose and galactose act synergistically in cataract production,[60] while supplements of ascorbic acid and phosphate fail to delay the effect. Rats fed a 35% galactose diet four days a week and starved on the other three develop cataracts in 40 days. If they are fed a normal diet on the three days but kept on the rest of the galactose regimen, cataracts do not form. This collection of evidence indicates that the carbohydrate effect is the direct cause of the lens changes and that it produces a block in some absorption mechanism. Patz[57] also showed the resumption of clear lens fiber production when experimental rats are taken off a galactose diet. Nordman and Mandel,[61] working with rat cataracts from high galactose intake and from alloxan diabetes, showed a reduction of adenosinetriphosphate. They suggest that energy necessary to keep the lens clear is made unavailable. Craig and Maddock,[62] using very high (70%) galactose diets, produced peripheral lens opacities in 9 days and central opacities in 20 days. They also found corneal vascularization, iritis, testicular atrophy, and hydronephrosis, with positive calcium and phosphorus balance and proteinuria. Tryptophan, up to 2%, failed to prevent the cataracts.

Alagna[63] gave rabbits alloxan diabetes and divided them into three groups. The control group developed typical diabetes and cataracts. A group started on vitamin E treatment before alloxan had less severe diabetes, and only one in six developed cataracts. A group treated with vitamin E after diabetes was established also had less severe diabetes, and three in eight developed cataracts. He concludes that vitamin E protects against alloxan diabetes and diabetic cataract.

Radiation Cataract.—Upton and his co-workers[64] studied radiation cataracts in mice to determine whether the effect was one of general irradiation or a local one. They found that irradiation of the whole mouse or of the head alone produced

cataracts while shielding of the head prevented lens changes, even with a much larger dose to the rest of the body. Alter and Leinfelder [65] carried localization studies further in rabbits. By shielding the lens and irradiating the ciliary body, and by shielding the ciliary body and irradiating the lens, they were able to show that direct lens exposure is necessary. Further, by exposing only quadrants of the lens, they produced quadrantic opacities. These studies confirm the hypothesis that radiation cataracts are produced through some direct alteration in the lens, whether chemical, enzymatic, physical, or cellular. They refute the idea of indirect impairment of nutrition supply.

The whole subject of radiation cataract is extensively reviewed and discussed by Ham.[66] He includes cyclotron, atom bomb, and accidental nuclear-reaction cataracts in humans, as well as experimental lens radiation studies.

Chemistry.—Dische and co-workers,[67] studying beef and rabbit lenses, found glutathione and various nucleotides in the capsule. The content is not altered by storage at low temperatures, but the isolated capsule rapidly oxidizes glutathione at room and body temperatures in the presence of oxygen. Ribose is broken down anaerobically. Since they found glutathione and nucleotides in the capsule separate from epithelium in about a third the concentration found in superficial lens tissue but very little in the aqueous, they conclude these substances are unable to leave the capsule surface. This suggests that the capsule is not as inert as connective tissue intercellular substance but that it actively regulates permeability.

Noting the high concentration of carbonic anhydrase in normal lenses and its reduction in senile cataracts, Reich and Healy [68] studied this enzyme in young, adult, and old bovine lenses, using a colorimetric measure of the rate of CO_2 hydration. They found no significant age difference and conclude that the decrease in enzyme activity is a result, not a causative factor, in cataract.

Also studying enzymes in the lens, Zeller [69] investigated catalase in dog, rabbit, and cattle lenses. He found a very small but definite amount of hydrogen-peroxide-decomposing capacity. Such small amounts were present that special methods had to be developed. The agent responsible is heat-labile and nondialyzable and is blocked by typical catalase inhibitors. There does not seem to be sufficient to protect against formation of hydrogen peroxide by ionizing radiation.

Harris, Gehrsitz, and Nordquist [70] studied the possibility of reversal of cation shift in the lens. Since normal lens has a high potassium and a low sodium content although bathed in fluid with high sodium and low potassium, and since cataracts show less difference, the possibility of reversal of this shift is important. They found the potassium loss and sodium gain under refrigeration reversed by raising the temperature. Glutamic acid enhances this recovery. Calcium deficiency degradation is reversed by adding calcium. The potassium and sodium concentration increase by incubation was found due to increases in total cation and dehydration.

Other chemical studies include the production of cataracts by intraperitoneal dopaquinone in guinea pigs on ascorbic-acid-free diet [71] and chromatographic studies of amino acids in ox lenses.§

Miscellaneous Studies.—Alvaro [74] discusses the paucity of our knowledge of lens opacities and stresses foci of infection. Auricchio [75] discusses cataracts in glaucoma, and Gozberk [76] tries to associate congenital cataracts and syphilis. Hunter and

§ References 72 and 73.

Lister [77] show colored illustrations of mercurial deposits in the lens. Jampolsky and Flom [78] report a case of anterior displacement of the lens and resultant transient myopia associated with the menstrual cycle. They do not explain the phenomenon.

Stone [79] outlines lens regeneration in the newt Triturus viridescens. When the lens is removed, a new one develops from dorsal iris epithelium. If the same lens is replaced or the lens of another species substituted, regeneration is inhibited. However, other tissues and foreign bodies, such as glass and wax spheres, do not inhibit regeneration. Repeated injections of aqueous from lens-containing eyes do cause inhibition, but repeated injection of Ringer's solution does not. Lens regeneration can be produced only by dorsal, and not by ventral, iris. It apparently takes place in this species whenever some non-species-specific inhibiting factor elaborated by lens is absent.

VITREOUS

A New Syndrome.—The most notable report on the vitreous is to be found in Irvine's Proctor Lecture.[80] In the course of his dissertation he summarizes recent concepts of the nature of the vitreous. Tracing its embryology and anatomy, he adds his own observations on Eye Bank eyes. He was able to confirm the observations of Vannas that the retrolental space contains fluid vitreous rather than aqueous and noted some elasticity of the hyaloid. He also noted a tendency of vitreous to weep fluid through an apparently intact hyaloid. Firm adhesions of the vitreous base to the ora serrata and pars plana were reconfirmed and less firm adhesions adhesions demonstrated at the optic nerve, macular area, and equator. In the background of the modern knowledge of vitreous structure, Irvine attempts to explain the "vitreous syndrome" which this paper describes. The syndrome consists of late rupture of the hyaloid and prolapse of vitreous into the anterior chamber after uneventful intracapsular cataract extraction. This is accompanied by irritability of the eye and followed by increasing adhesions of vitreous to the undersurface of the wound. Vitreous opacities form in radiating fashion from the adhesions toward the pupillary space. Late recondensation of the hyaloid occurs, forming a lobulated mass in the pupil and strands of adhesions to the undersurface of the wound. Late macular changes may accompany this sequence of events and cause visual loss. The adhesions which are the essence of this syndrome are not noted until weeks or months after the operation. Irvine believes that this sequence of events, in whole or in part, occurs oftener than is recognized. In a series of 894 intracapsular extractions, 23% showed late rupture of the hyaloid, with 8% going on to wound adhesions. Histological sections, clinical illustrations, and statistical details are presented. An explanation is offered as follows [80]:

1. Rupture of the vitreous face due to weakness of the hyaloid, and partly due to action of the pupil on the herniated prolapse.

2. Then release into the anterior chamber of varying amounts of free vitreous, some of which is in a state of aggregation and appears as a gel and some of which may be transparent fluid vitreous.

3. The vitreous coming in contact with the under surface of the wound, which remains incompletely healed for a much longer time than is generally realized.

Vitreous Opacities and Hemorrhages.—Rudwan [81] treated posthemorrhagic and postuveitis vitreous opacities by weekly intravenous injections of 500 ml. of plasma.

Five patients out of six seemed to improve slowly. He credits the plasma, rather than time, with the improvement. Havenar and Falls [82] injected cholesterol into rabbit vitreous but were unable to influence the opacities by intensive treatment with lipotropic substances. Lepri [83] and Alajmo and Ambrosio [84] treated vitreous hemorrhages with streptokinase-streptodornase preparations. The first author reported improvement after orbital injections in two patients and good tolerance of the rabbit to subconjunctival, anterior chamber, and orbital injections. The others reported no effect from orbital or subconjunctival injections. They found that only ineffectual doses were well tolerated and that larger doses produced violent reactions and corneal opacities.

Cross and Choyce [85] report an unusual case of recurrent vitreous hemorrhage in which the lens became dislocated backward by organization of clots. Extensive staphyloma formed in spite of normal tension. Korenevich [86] reports good results from discission of cloudy anterior vitreous following hemorrhage. He performed these discissions anteriorly in aphakia or from behind when the lens was present.

Structure.—Surgiura [87] passed bovine vitreous through glass filters and studied the residue by x-ray diffraction. The similarity of interference lines to those found in cornea suggest similarities in chemical structure. Cagianut and Wunderly [88] obtained fresh human vitreous immediately after enucleation in four cases and made studies by paper electrophoresis and ultracentrifugation. They found a homogeneous albumin as 60 to 80% of the total protein. They could determine no macroglobulins, but only components of normal molecular size. There was no important change in the protein fraction in glaucoma. Kock [89] describes two kinds of filaments in fish vitreous with characteristic micellar structure.

Rossi,[90] in contrast to other investigators, stated that filamentary structures in the vitreous were all artifacts. By phase-contrast microscopy he was unable to find fibrous structure in fresh rabbit vitreous, but noted only crystal-like formations. He did find fibrils after storage or fixation. He suggests that most studies have been confused either by such factors or by getting zonular fibrils mixed with vitreous. This assertion is as yet unsupported.

Miscellaneous.—Adamantiadis [91] reports posterior annular vitreous detachment as a common occurrence, and not necessarily a prelude to retinal separation. Bisland [92] reports six cases of vascular loops in the vitreous and outlines reasons why they are not related to remnants of the hyaloid artery, retrolental fibroplasia, or posthemorrhagic or inflammatory vascularization.

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News and Comment

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Home Study Courses, American Academy of Ophthalmology and Otolaryngology.—The Home Study Courses in the basic sciences related to ophthalmology and otolaryngology, offered as a part of the educational program of the American Academy of Ophthalmology and Otolaryngology, will begin on Sept. 1 and continue for a period of 10 months. Registrations must be completed before Aug. 15. Detailed information and application forms may be secured from Dr. William L. Benedict, the executive secretary-treasurer of the Academy, 100 First Avenue Building, Rochester, Minn.

International Congresses of Ophthalmology in São Paulo, Brazil, June, 1954.—The following ophthalmological congresses will be held in São Paulo, June 9 to 17, 1954: Third Pan-American Interim Congress of Ophthalmology, Pan-American Congress for the Welfare of the Blind, Second Congress of the South American Meridional Ophthalmological Society, Eighth Brazilian Congress of Ophthalmology, and an International Congress of Oto-Neuro-Ophthalmology.

The official subjects for the Pan-American Congress are Recent Advances in Ocular Therapeutics and Prevention of Blindness. The official subjects for the Eighth Brazilian Congress are Uveitis and Keratoplasty.

Registration in one congress implies the right to take part in all the scientific and social activities of the other meetings.

The Registration fee is $10. Members of the Pan-American Association of Ophthalmology will be granted a 30% rebate.

For information, please write to the president of the Pan-American Association of Ophthalmology, Prof. Moacyr E. Alvaro, 1151 Consolação, São Paulo, Brazil; telegraphic address, "Ophthalmos."

Research Fellowship in Ophthalmology, Indiana University Medical Center.—Information regarding a Research Fellowship in Ophthalmology at Indiana University Medical Center may be obtained by writing to Dr. T. F. Schlaegel Jr., 1100 W. Michigan St., Indianapolis 7. It is not necessary to have had training in ophthalmology to be accepted for this position. For those who have not had a graduate course in ophthalmology, the fellowship will provide some training prior to a residency. Fellows assist in the eye clinic and at eye surgery and attend the formal classes for eye residents. The stipend is $1,800 per year, plus room and laundry.

The American Orthoptic Council.—The annual examination of orthoptic technicians by the American Orthoptic Council will be conducted in July and September, 1954.

The written examination will be nonassembled and will take place on Thursday, July 22, in certain assigned cities and offices, and will be proctored by designated ophthalmologists.

The oral and practical examinations will be on Saturday, Sept. 18, in New York, just preceding the meeting of the American Academy of Ophthalmology and Otolaryngology.

Applications for examination will be received by the office of the secretary of the American Orthoptic Council, Dr. Frank D. Costenbader, 1605 22d St. N.W., Washington 8, D. C., and must be accompanied by the examination fee of $30. Applications will not be accepted after June 1, 1954.

PERSONAL NEWS

Leslie Dana Gold Medal Awarded.—The Leslie Dana Gold Medal, awarded annually by the St. Louis Society for the Blind for outstanding achievements in the prevention of blindness and the conservation of vision, was conferred upon Mrs. Audrey H. Gradle, Sherman Oaks, Calif., at a conference luncheon of the National Society for the Prevention of Blindness in St. Louis, on Thursday, March 11.

Setting a new precedent for Pan-American cultural relations in ophthalmology, Drs. William B. Clark, Howard F. Hill, and Paul Chandler, as a team, visited Cuba and Puerto Rico, where, at the invitation of the local ophthalmological societies, the following program was given:

Selection and Preparation of the Patient for Cataract Extraction. Dr. William B. Clark

Incision and closure. Dr. Howard F. Hill

Management of the Immediate and Postoperative Complications of Cataract Surgery. Dr. Paul Chandler

Round-table questions and answers

SOCIETY NEWS

Irish Ophthalmological Society.—The annual meeting of the Irish Ophthalmological Society will be held in Dublin on April 29 and 30 and May 1, 1954.

The Montgomery Lecture, entitled "Some Recent Contributions to the Diagnostic Problem of Glaucoma," will be delivered by Professor Bietti, Parma, Italy.

West Virginia Academy of Ophthalmology and Otolaryngology.—The West Virginia Academy of Ophthalmology and Otolaryngology will hold its next regular meeting at The Greenbrier Hotel, White Sulphur Springs, W. Va., May 27-29, 1954.

Books

Diseases of the Retina. By Herman Elwyn. Second Edition. Price, $12.00. Pp. 696, with 243 illustrations, 20 in color. The Blakiston Company, Inc., 575 Madison Ave., New York 22, 1953.

Many important changes have been made in the second edition of this excellent text on diseases of the retina. The chapter on diabetic retinopathy is especially well done, and could be read with profit not only by ophthalmologists but by all internists treating this disease. The chapters on the angiospastic diseases have likewise received considerable revision. Many of the ideas expressed are original with the author and run counter to those held by internists working in this field. This does not detract from, but rather adds to, the value of the book when read by the advanced student, in that the last word has certainly not been said on the pathogenesis of either essential hypertension or those other conditions, like diffuse glomerulonephritis and the kidney of pregnancy, that result in a similar fundus picture. A chapter has been added on retrolental fibroplasia, and important work of Woods and his associates on ocular tuberculosis makes this chapter an excellent review of ocular tuberculosis in general.

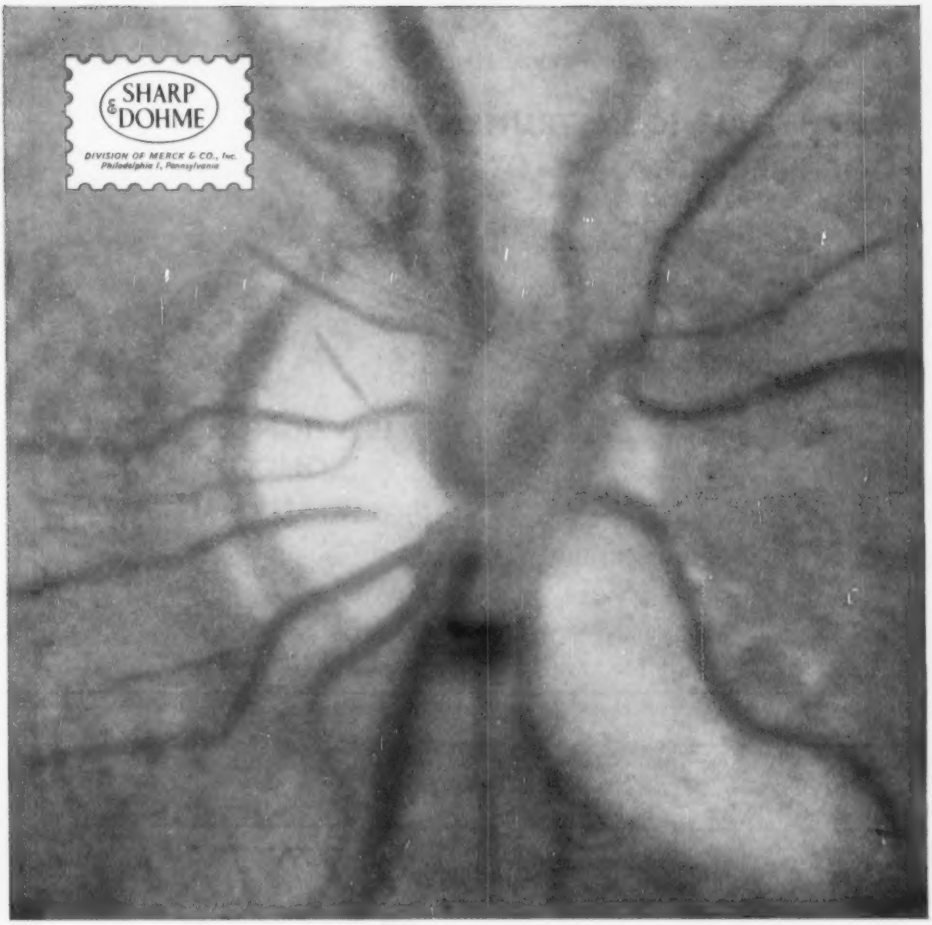
There are good bibliographies at the end of each chapter, and the illustrations are all that could be desired.

Eleven Blue Men—And Other Narratives of Medical Detection. By Berton Roueché. Price, $3.50. Pp. 215. Little, Brown & Company, 34 Beacon St., Boston 6, 1954.

Here is a treat for the tired ophthalmologist, too weary from the day's labor to concentrate on the effects of 17-hydroxycorticosterone on ocular pathology but too mentally alert to yield to the usual detective story. This is the compromise. It presents twelve short, but fascinating, tales of medical detection, superbly written by one of *The New Yorker's* best writers, Berton Roueché.

For two of these stories, "A Pig from New Jersey," which relates how Dr. Lawrence Levy, of the Bureau of Preventable Diseases, traced the source of the contaminated meat in a group of cases of trichinosis, and "The Fog," which details the nightmarish story of the smog at Donora, Pa., which in October, 1948, struck down half the town's population and killed twenty, the author was awarded the 1950 Lasker Foundation Award for medical reporting.

All of these stories are interesting and instructive. They combine the excitement of the search for a criminal with the satisfaction that comes from learning what is going on in other fields of medical endeavor. As a prescription, one a night before turning out the light will be found very rewarding.



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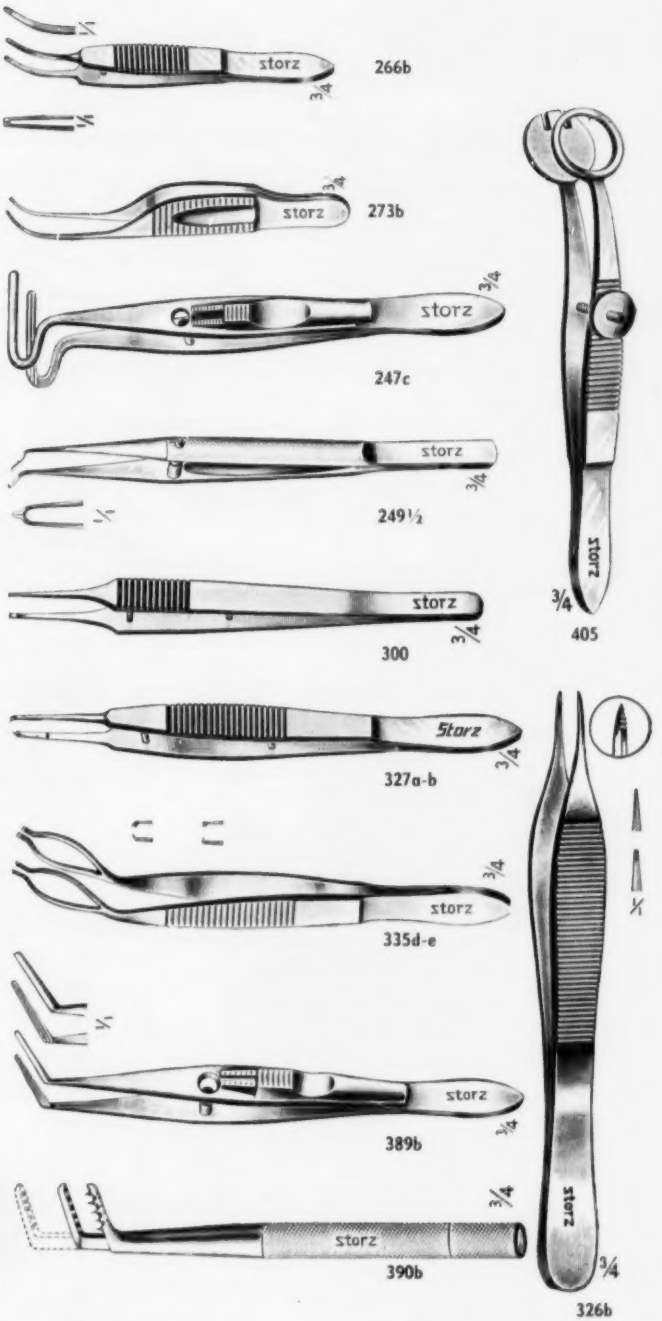

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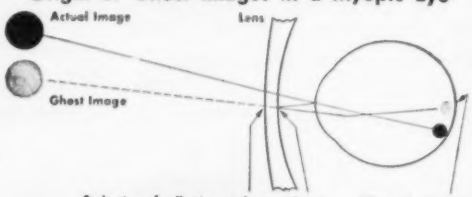

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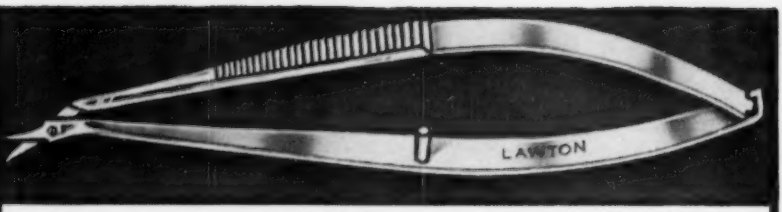

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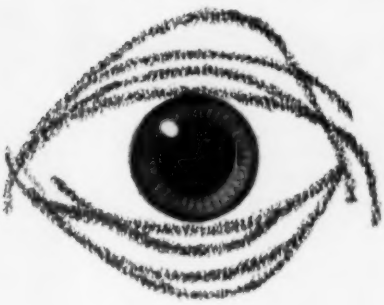

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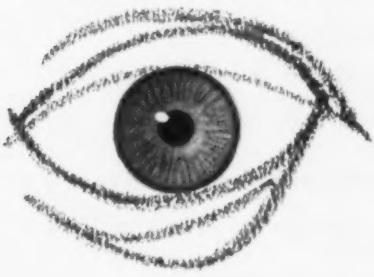

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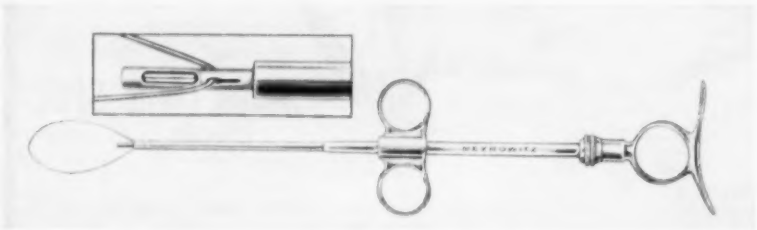

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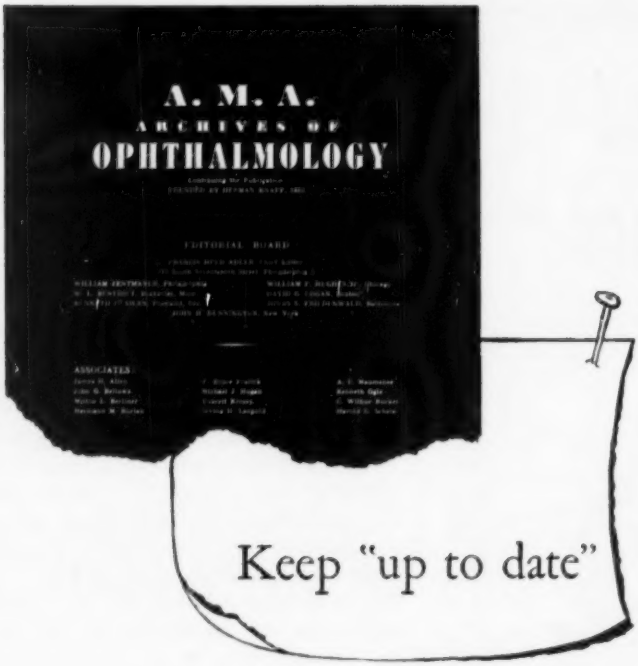

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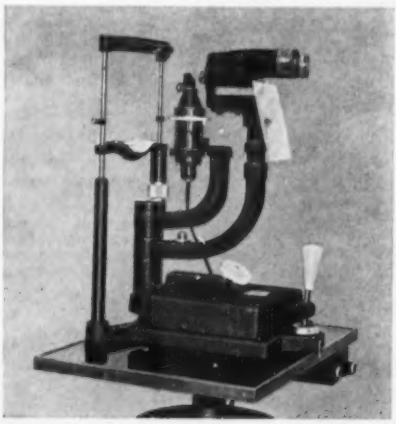

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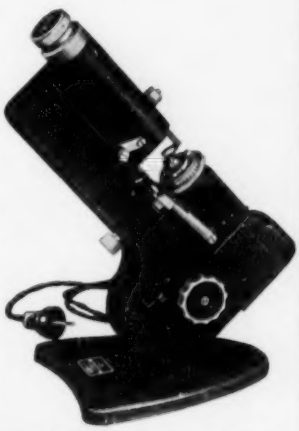

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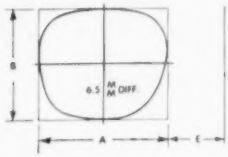

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